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

Revised Draft:
Report on Carcinogens
Monograph on Trichloroethylene

October 24, 2014

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 12th 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 its 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), genotoxicity 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). The information in Section 7 is a synthesis of Sections 1 through 6.

The information reviewed in Sections 1 through 7 (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. Two written public comments on trichloroethylene were 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 484 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

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.

(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. Any discrepancies between the two reviewers were resolved by mutual discussion in reference to the original data source. 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, 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.

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Peer Review

Peer review of the Draft RoC Monograph on Trichloroethylene was conducted by an *ad hoc* expert panel at a public meeting held August 12, 2014, in the Rodbell Auditorium at the National Institute of Environmental Health Sciences, David P. Rall Building, Research Triangle Park, NC (see http://ntp.niehs.nih.gov/go/38854) for materials, minutes, and panel recommendations from the peer review meeting). The selection of panel members and conduct of the peer review were performed in accordance with the Federal Advisory Committee Act and Federal policies and regulations. The panel members served as independent scientists, not as representatives of any institution, company, or governmental agency.

The charge to the Peer-Review Panel was as follows:

1. To comment on the draft cancer evaluation component for trichloroethylene, specifically, whether it was technically correct and clearly stated, whether the NTP has objectively presented and assessed the scientific evidence, and whether the scientific evidence is adequate for applying the RoC listing criteria,

2. To comment on the draft substance profile for trichloroethylene, specifically, whether the scientific justification presented in the substance profile supports the NTP's preliminary policy decision on the RoC listing status of the substance.

1. The Panel was asked to vote on the following questions:

2. Whether the scientific evidence supports the NTP's preliminary conclusion on the level of evidence for carcinogenicity from human cancer studies for each of the three cancer sites: kidney cancer non-Hodgkin lymphoma (NHL), and liver cancer.

3. Whether the scientific evidence supports the NTP's preliminary listing decision for trichloroethylene in the RoC.

This RoC monograph on trichloroethylene has been revised based on NTP's review of the Panel's peer-review comments. The Peer-Review Panel Report, which captures the Panel recommendations for listing status of trichloroethylene in the RoC and their scientific comments, and the NTP Response to the Peer-Review Report are available on the Peer-Review Meeting webpage for trichloroethylene (http://ntp.niehs.nih.gov/go/38854).

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Part 1

Draft Cancer Evaluation

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Introduction

Trichloroethylene is a volatile chlorinated alkene used mainly as an intermediate in hydrofluorocarbon production as a degreaser for metal parts (EPA 2014). Other uses for trichloroethylene include use in clear protective spray coatings for use by arts and crafts hobbyists and as a modifier for polyvinyl chloride polymerization. Use of trichloroethylene as a degreaser in the United States declined beginning in the 1970s (Bakke *et al.* 2007).

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 and oral 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.

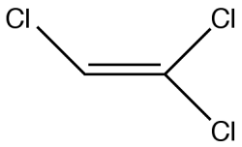

Figure 1. Chemical structure of trichloroethylene

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 principal 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/hour (hand immersion) and 0.019 cm/hr (patch) in water and 0.0074 cm/hour (hand immersion) and 0.0043 cm/hour (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/hour (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 (Bartoníček 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/hour, 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 than 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 with 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.

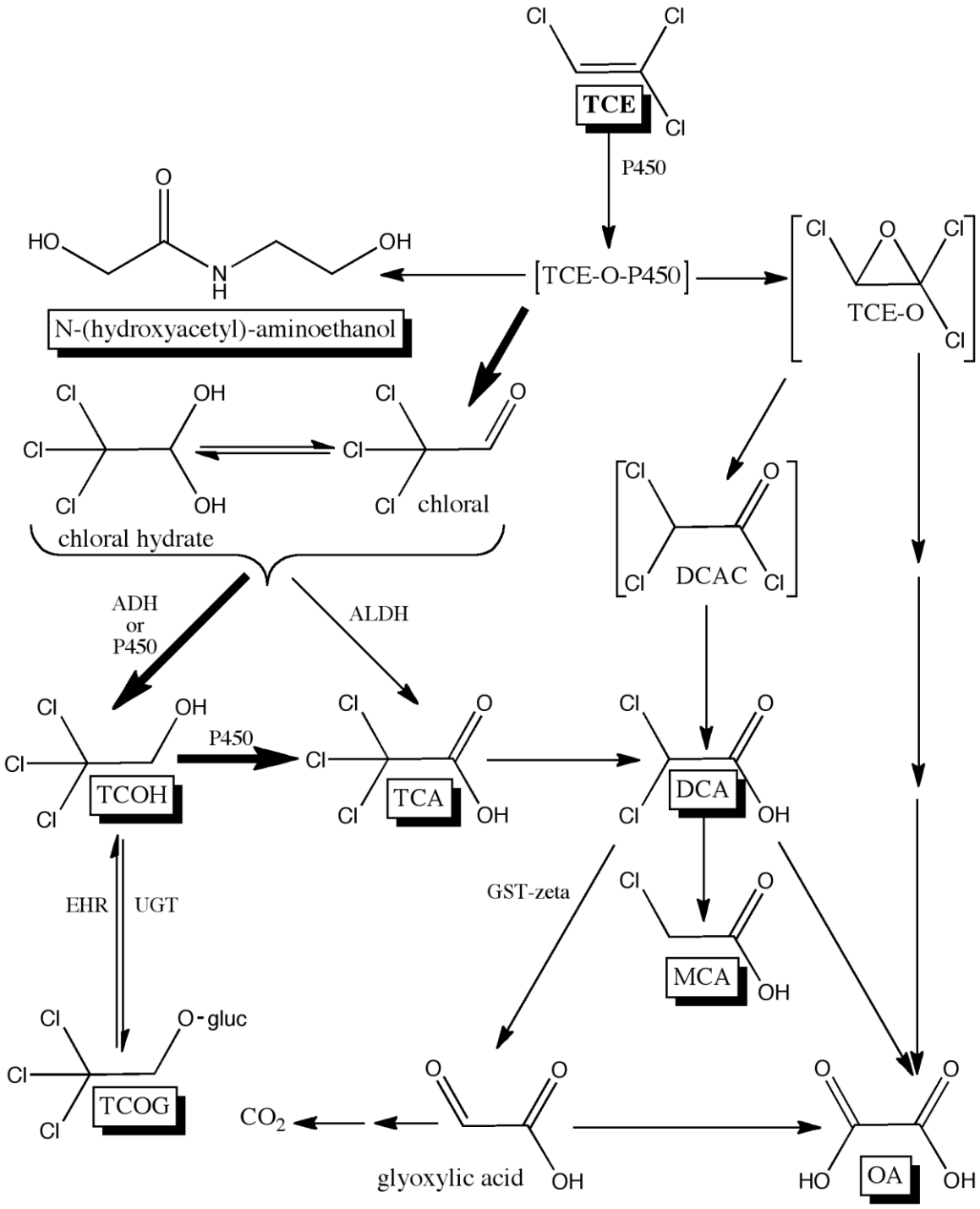

Figure 1-1. Oxidative metabolism of trichloroethylene (TCE)

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. Heavy arrows indicate primary pathways. 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 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.* 1997a); however, two recent studies reported no association (Yang *et al.* 2013, Liu *et al.* 2012).

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 with 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 with 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.* (2011) showed that the levels of DCVG and DCVC were much lower than oxidative metabolites and varied considerably with strain.

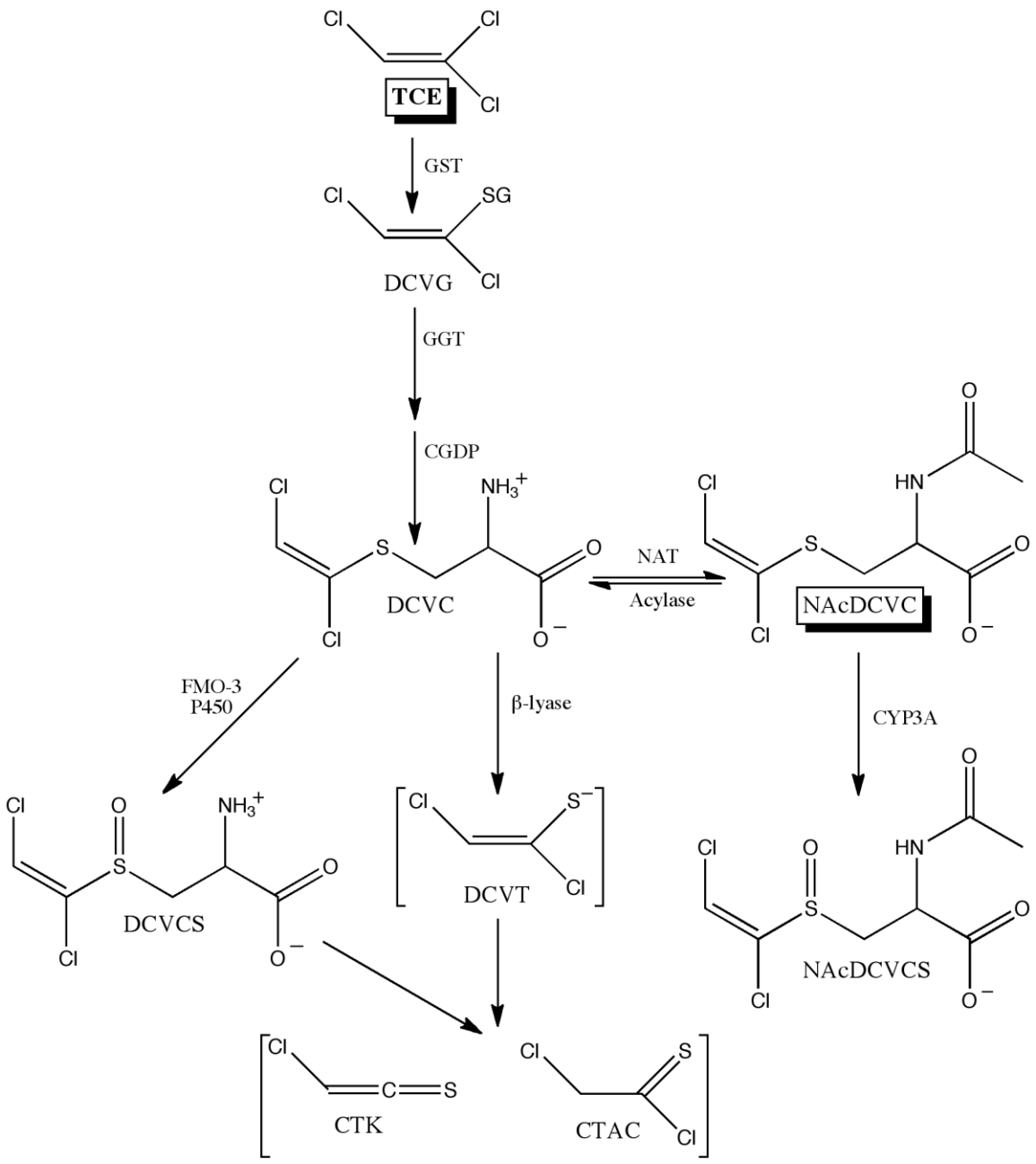

Figure 1-2. Glutathione-dependent metabolic pathways of trichloroethylene*

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 lung testes	yes yes yes	yes yes yes	no
CH/CHL	liver lung testes	yes yes yes	yes yes yes	yes
TCOH	liver lung GI testes	yes – yes yes	yes yes yes yes	yes
TCA	liver lung testes	yes yes yes	yes yes –	yes
TCOG	liver	yes	yes	yes
DCA	liver lung testes	– – yes	yes yes –	yes (low amount)
GSH-conjugation				
DCVG, DCVC	liver kidney	yes yes	yes yes	yes
DCVT, DCVCS, CTK/CTAC	kidney hematopoietic	yes –	yes yes	no
NAcDCVC, NAcDCVS	liver kidney	yes yes	yes 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). However, serum concentrations of DCVG and DCVC collected from rats exposed to an oral dose of 1,970 mg/kg (Lash *et al.* 2006) were comparable (i.e., within an order of magnitude) to those obtained in mice exposed to an oral dose of 2,140 mg/kg in a more recent study (Kim *et al.* 2009a,b).

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) in this study but elimination half-lives were similar. Based on an analysis of the distribution of individual values for DCVG in blood the results could indicate the existence of two subpopulations of individuals with a genetic polymorphism rather than a true gender difference. 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.

EPA (2011a) developed an updated physiologically based pharmacokinetic model (PBPK) for trichloroethylene and its metabolites. A hierarchical Bayesian population analysis using Markov chain Monte Carlo sampling was performed to evaluate uncertainty in population parameters and variability within a population. Simulations for a number of representative dose-metrics across species were conducted to predict the fraction of trichloroethylene metabolized by oxidative or GSH-conjugation pathways (liver and kidney) under conditions of continuous inhalation or oral exposure. Results from these simulations for humans show that the fraction metabolized by oxidation decreases at higher doses while the fraction metabolized by GSH-conjugation increases with dose (Figures 1-3 and 1-4).

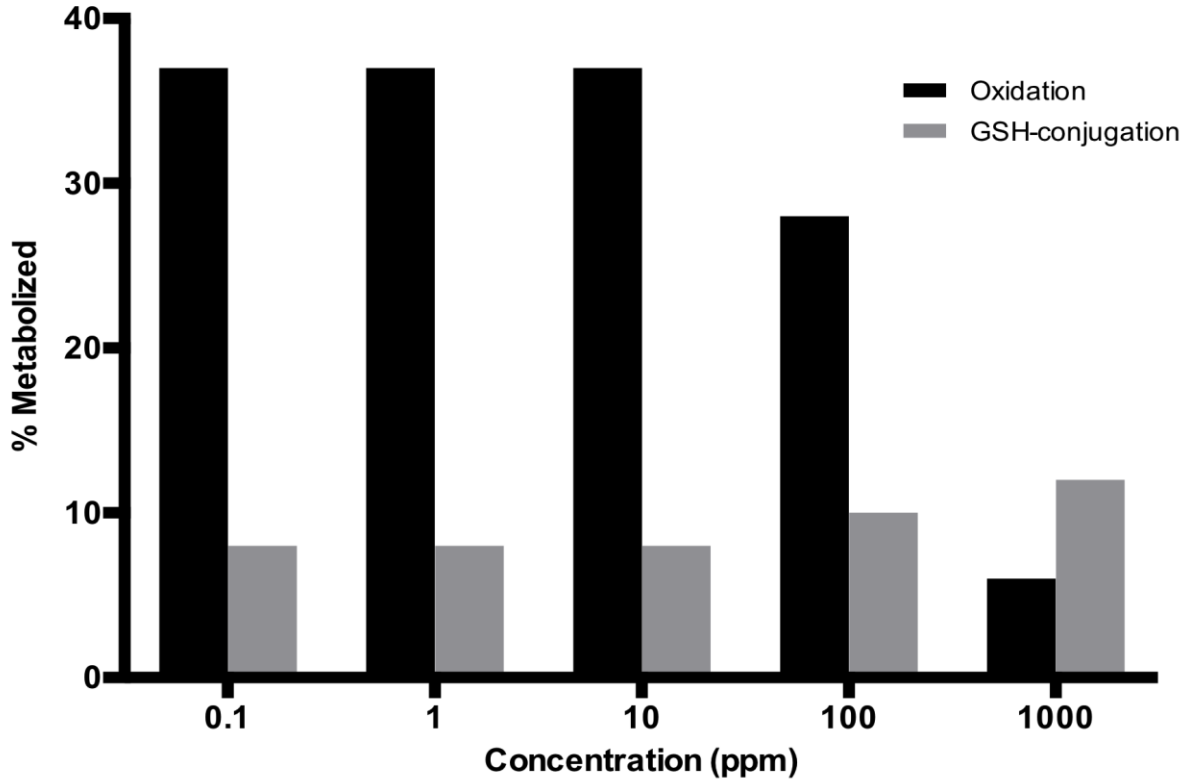

Figure 1-3. PBPK model predictions for the fraction of trichloroethylene intake that is metabolized under continuous inhalation exposure in humans.

Source: EPA 2011a.

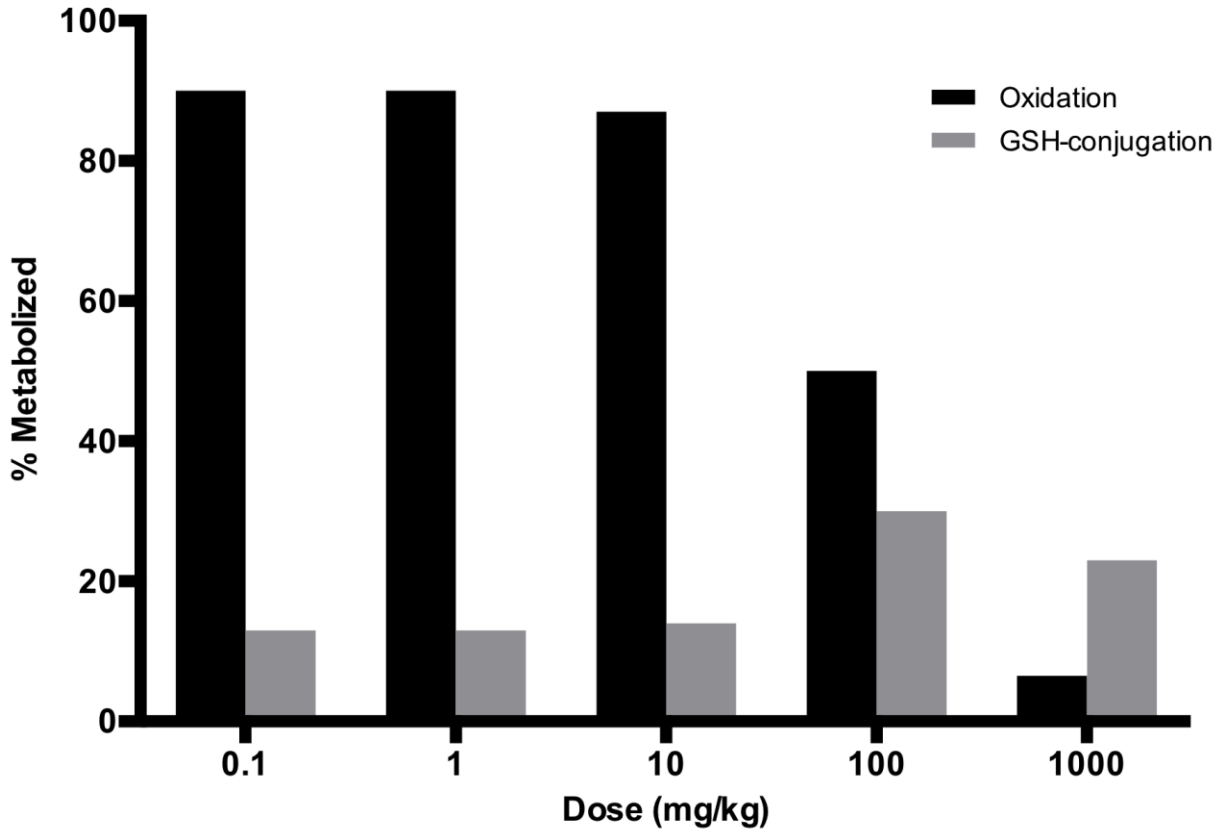

Figure 1-4. PBPK model predictions for the fraction of trichloroethylene intake that is metabolized under continuous oral exposure in humans.

Source: EPA 2011a.

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 generally smaller 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 intra- and interspecies 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 Genotoxicity and related effects

This section addresses genotoxicity 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. Related effects, such as cell transformation and DNA and protein binding, are included in the review when data were available.

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 2014, 1995, EPA 2011a, NAS 2006) 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, chemical volatility and solvent use. 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 informed by the study design and reporting; e.g., it is possible that an impure test sample could result in a 'positive' result that is actually due to a contaminant. For example, when epichlorohydrin or 1,2-epoxybutane is present as a stabilzer in the test sample of trichloroethylene, an observed mutagenic response could actually be due to those chemicals rather than to the trichloroethylene. Conversely, false 'negative' results could occur if the study design is not optimal; the use of inappropriate treatment methods or assay type could compromise the results. For example, a volatile chemical may test "negative" in a standard mutagenicity assay but "positive" when the assay is modified for testing vapor phase samples. In addition, solvents such as DMSO can chemically react with test chemicals, including raising the pH, and result in effects that would not otherwise be observed; thus, careful consideration should be made of assays in which reactive solvents are used.

Results from studies on the genotoxic effects of trichloroethylene are summarized in tables in Appendix C and an overall summary call is provided by endpoint in Table 2-1, based on the integration of the evidence from authoritative reviews (IARC 2014) and any additional studies identified.

2.1 *In vitro* mutagenicity studies of trichloroethylene in bacteria

Trichloroethylene exposure induced mutants in *Salmonella typhimurium* tester strain TA100 in several, but not all, studies that tested pure (no stabilizer) samples of trichlorethylene. Although results in other strains (TA97, TA98, and TA1537) were negative, the positive results in stain TA100 are attributed to base-pair substitution and thus provide some evidence for mutagenicity

of trichloroethylene in the presence of metabolic activation (IARC 2014). Results from these studies are discussed below and summarized in Appendix C, Table C-1.

Trichloroethylene without stabilizers (high purity) induced a slight, but reproducible, response in most, but not all, studies using *Salmonella* strain TA100, with the addition of exogenous metabolic activation (S9). Of the five positive studies in TA100 that tested samples without stabilizers, only one used DMSO as a solvent (see Section 2.7.1 for a discussion of the potential interaction between DMSO and TCA), suggesting that the solvent used did not affect the results. Trichloroethylene was weakly positive in one study with strain TA1535, tested without S9. A negative response was noted for all other strains, either with or without S9. Different tester strains of *Salmonella* are designed to detect the type of mutation that is induced. Negative results in TA97, TA98, and TA1537 suggest that trichloroethylene do not induce frameshift mutations while the positive results observed for strains TA1535 and TA100 are attributed to base-pair substitution. In addition, strain TA100 was derived from TA1535 with the addition of plasmid pKM101, which makes it more sensitive and could explain the results observed with these two strains. 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 (McGregor *et al.* 1989). 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 a reversion assay using *E. coli* K12, but only with the addition of metabolic activation; however, DMSO was used in this study. Furthermore, the use of certain solvents (e.g., DMSO, ethanol) can be a concern if they chemically interact with the test compound (see discussion in Section 2.7.1) or affect key metabolizing enzymes such as CYP2E1, which can lead to false negative results.

Mutagenicity studies of trichloroethylene in wastewater suggest that the parent compound or its metabolites interact with other chemicals present in the water to enhance the genotoxicity of complex mixtures, based on the results from tests with trichloroethylene alone or in the wastewater. In a study by Tabrez and Ahmad (2012), wastewater samples contaminated with trichloroethylene (determined by gas chromatography analysis to be 28.4 and 8.97 mg/L were mutagenic in the Ames fluctuation assay using *S. typhimurium* strains TA98 and TA100. The authors reported that exposure to trichloroethylene alone at concentrations up to 1,000 mg/L did not induce mutations in the assay. 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.

2.2 *In vitro* genotoxicity studies of trichloroethylene in non-mammalian eukaryotes

Results of *in vitro* genotoxicity studies of trichloroethylene in non-mammalian eukaryotes are summarized in Appendix C, Table C-2. Positive effects were observed in several studies, for both pure (no stabilizers) test samples and those of unknown purity; none of these studies used DMSO as a solvent. 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. There is some evidence that trichloroethylene causes gene conversion and gene mutation in *Saccharomyces cerevisiae* D7 in the presence of

metabolic activation. Evidence for gene conversion comes from positive finding in two of three studies (Bronzetti *et al.* 1978, Callen *et al.* 1980), one of which used trichloroethylene that did not contain stabilizers (Bronzetti *et al.*); findings were negative in strain D4, which has a lower content of CYP then strain D7. Trichloroethylene exposure caused gene mutations in all three studies in *S. cerevisiae* D7 including one study using a preparation that did not use stabilizers, and in actively growing (not quiescent) cultures of the mold *Aspergillus nidulans* (Crebelli *et al.* 1985). However, trichloroethylene was not mutagenic in the yeast *Schizosaccharomyces pombe*, either with or without S9 activation (Rossi *et al.* 1983). Trichloroethylene also caused aneuploidy in *S. cerevisiae* D7 (with and without activation) and recombination and mitotic crossover in *S. cerevisiae* D7 (with metabolic activation) but not in quiescent or growing *A. nidulans* cells. Interpretation of these endpoints is limited because purity of trichloroethylene is not known in any of the studies.

In the study of wastewater genotoxicity described above, wastewater samples alone (which were contaminated with trichloroethylene) 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).

2.3 *In vitro* studies of genotoxicity and related effects of trichloroethylene in mammalian cells

Several studies have examined the potential for trichloroethylene-induced genotoxicity in mammalian systems *in vitro*; findings are discussed below and summarized in Appendix C, Table C-3. These studies suggest that trichloroethylene causes genotoxicity *in vitro*, specifically DNA strand breaks, micronucleus formation, and sister chromosome exchanges *in vitro*. Importantly, some of these effects (DNA strand breaks and micronuclei) were observed in the kidney. A limitation of these studies is that, for many of them, the purity of trichloroethylene is unknown. Regarding the use of DMSO as a solvent in these studies, it does not appear to be a confounding issue. Very few studies included exogenous metabolic activation and the only two studies that reported positive results apparently used DMSO as a solvent. However, several assays reporting positive results were conducted using primary cells, which presumably have retained endogenous metabolic capability, and most of these studies did not use DMSO as a solvent. In addition, trichloroethylene also caused cell transformation, which can arise from genotoxic and non-genotoxic mechanisms.

Trichloroethylene exposure induced dose-dependent increases in 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); these results may be due to trichloroethylene metabolites since cultured primary cells generally retain endogenous metabolic activation capabilities. However, there was also a significant increase in micronuclei in CHO-K_1 cells treated with trichloroethylene (> 99.5% pure) without the addition of exogenous S9, suggesting metabolism was not needed for the observed effect (Wang *et al.* 2001) but not in human lymphocytes (Kumar *et al.* 2009). *In vitro* trichloroethylene exposure increased the frequency of sister chromatid exchange (SCE) in mammalian cells in two studies using pure

samples (Galloway *et al.* 1987, Gu *et al.* 1981); a short exposure time, limited dose levels, and lack of a positive control limit the interpretation of the results of the third study (White *et al.* 1979). Trichloroethylene exposure 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).

Findings were inclusive for gene mutation; increased mutations were observed in mouse lymphoma cells treated with trichloroethylene (in the presence, but not absence, of exogenous metabolic activation S9); however, mutation was not reported in treated human TK6 cells, with or without S9 (Caspary *et al.* 1988). Results for trichloroethylene induction of unscheduled DNA synthesis (UDS) were negative in rat and mouse hepatocytes when pure samples were tested (Shimada *et al.* 1985, Williams *et al.* 1989), but results were mixed when test samples of trichloroethylene contained stabilizers or were of unknown purity (Costa and Ivanetich 1984, Shimada *et al.* 1985, Williams *et al.* 1989, Milman *et al.* 1988). A study in human lymphocytes showed a weak response for UDS induction after exposure to trichloroethylene; although the test sample presumably did not contain stabilizers and the DMSO concentration was only 1% (IARC 2014).

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). Cell transformation assays may not indicate a genotoxic mechanism.

2.4 Studies of nucleic acid and protein binding of trichloroethylene

Binding of trichloroethylene to nucleic acids and proteins has been studied in cell-free systems and *in vivo* in rodents and are discussed below and summarized in Appendix C, Table C-4. The available evidence shows that trichloroethylene can bind both DNA and protein. None of the reviewed studies reported using DMSO as a solvent.

In vitro 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, Bergman 1983, Miller and Guengerich 1983, Mazzullo *et al.* 1992), and rat and mouse hepatocyte DNA (Miller and Guengerich 1983). Binding was observed in microsomal proteins from mouse and rat liver, lung, stomach, and kidney (Banerjee and Van Duuren 1978, Miller and Guengerich 1983) and human liver (Miller and Guengerich 1983). All but one of these *in vitro* studies used test samples that did not contain stabilizers; Mazzullo *et al.* (1992) used 98.9% pure trichloroethylene, which may have contained stabilizers or impurities (IARC 2014). Studies showing significant binding of trichloroethylene metabolites to DNA and protein 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 (Cai and Guengerich 2001) and, to a lesser extent, DNA (Miller and Guengerich 1983). Phenobarbital pretreatment increased the formation of the trichloroethylene metabolites chloral hydrate (CH) and trichloroethylene oxide and increased the formation of DNA and protein adducts (Miller and Guengerich 1983).

Studies *in vivo* provide evidence of binding to protein and DNA in both mice and rats following trichloroethylene administration. Protein binding was observed in both liver and kidney from B6C3F1 mice but not Osborne-Mendel rats exposed to trichloroethylene by inhalation (Stott *et al.* 1982). In the same study, results for DNA binding in the liver for mice treated orally were inconclusive. However, a second study reported weak DNA binding in the liver, kidney, lung, and stomach of both the BALB/c mouse and the Wistar rat exposed to TCE by i.p. injection; test sample purity was 98.9% (Mazzullo *et al.* 1992). NMRI mice treated i.p. with trichloroethylene (≥ 99% pure) showed increased radioactivity in nucleic acids for several tissues (spleen, lung, kidney, pancreas, testis, and brain), this effect was due to the metabolic incorporation of ^{14}C-labeled nucleotides directly into DNA and RNA, especially guanine and adenine, rather than adduct formation (Bergman 1983).

2.5 *In vivo* genotoxicity studies in rodents

Trichloroethylene has been tested for genotoxicity *in vivo* and study results are discussed below and summarized in Appendix C, Table C-5. Overall, there is some evidence that trichloroethylene can induce DNA strand breaks and micronucleus formation, depending on the tissue, in rodents. These two endpoints are consistent with *in vitro* studies, and similar to *in vitro* studies, positive findings were observed in the kidney. Studies on the effects of trichloroethylene exposure at other endpoints, including gene mutation, chromosomal aberrations, SCE, and UDS, were all negative (see Table C-5 and IARC 2014). DMSO was probably not used in any of the studies (there were only two studies where its use was unknown).

Trichloroethylene caused DNA strand breaks in liver in a study in rats (Nelson and Bull 1988) and in two of three studies in mice (Nelson and Bull 1988, Robbiano *et al.* 2004, Parchman and Magee 1982). Findings in kidney were positive in the mouse (Walles 1986) but inconsistent in the rat. Robbiano *et al.* (2004) reported positive findings in the rat kidney after a single exposure to 3,591 mg/kg trichloroethylene (reagent grade purity) by oral administration, while a 5-day 2,000-ppm inhalation study (99.5% pure test sample, no information on stabilizers) yielded negative results (Clay *et al.* 2008). Differences do not seem to be explained by dose because the dose from the inhalation exposure may have been higher than the oral dose. Estimated inhalation exposure is 10,800 mg/kg/day assuming 100% absorption, which is most likely lower at high exposures, such as 2,000 ppm, and thus would result in a lower estimated mg/kg/day dose.

Trichloroethylene exposure *in vivo* induced micronucleus formation in kidney cells of rats treated orally (Robbiano *et al.* 2004). For rats treated by inhalation, one study reported dose-related micronucleus induction in bone marrow erythrocytes after a single inhalation exposure; the authors replicated the findings in a subsequent one-dose experiment (Kligerman *et al.* 1994). No increased in micronucleus formation was observed in a four-day inhalation exposure by the same authors; however, the authors noted that the micronucleus formation in the concurrent controls was unusually high. A negative finding was reported in a single inhalation exposure study by a different author (Wilmer *et al.* 2014). All of the studies used trichloroethylene exposure without stabilizers. No increase in micronucleus formation was observed in peripheral blood lymphocytes after inhalation exposure (Kligerman *et al.* 1994). In studies in the mouse, there was micronucleus induction in the bone-marrow erythrocytes of exposed animals in two of four studies (Duprat and Gradiski 1980, Hrelia *et al.* 1994; Shelby *et al.* 1993, Kligerman *et al.* 1994), which used different routes of exposure (inhalation, i.p. and p.o.) and strains of mice. One study reported a correlation with urinary TCOH, which strengthens the findings (Hrelia *et al.*

1994). No increase in micronuclei was observed in either splenocytes or spermatocytes from mice exposed to trichloroethylene by inhalation (Kligerman *et al.* 1994, Allen *et al.* 1994).

2.6 Studies of genotoxicity in humans exposed to trichloroethylene

A few studies have examined cytogenetic endpoints in peripheral blood lymphocytes of trichloroethylene-exposed workers, including one that evaluated chromosomal aberrations and three that measured SCEs. Findings from these studies are discussed below and summarized in Appendix C, Table C-6.

In addition, several case-control studies of renal-cell cancer 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 database on cytogenetic studies is inadequate to evaluate conclusively because it is limited by small numbers of exposed workers in a few studies. 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.* (1981) measured a statistically significant increase in SCE in 6 exposed workers, no increase 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).

2.7 Genotoxic and related 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), trichloroethanol (TCOH), dichloroacetic acid (DCA), chloral hydrate (CH), *S*-(1,2-dichlorovinyl)-L-cysteine (DCVC), *S*-(1,2-dichlorovinyl)glutathione (DCVG) and *N*-acetyl DCVC (NAcDCVC). Information is available for all of these metabolites, but is limited to a few studies for TCOH, DCVG, and NAcDCVC. Results on the genotoxic effects of trichloroethylene metabolites are summarized in Table 2-1 and are based on the integration of the evidence provided from the authoritative reviews (IARC 2014), as well as any additional studies identified. A 2000 review of genotoxicity information for trichloroethylene and its metabolites discussed the mutagenic potency of trichloroethylene metabolites and reported that the oxidative metabolites required very high doses to induce an effect (Moore and Harrington-Brock 2000). In their evaluation, DCVC was the most potent mutagen while TCA was the least potent mutagen.

2.7.1 Trichloroacetic acid (TCA)

Overall, there is weak evidence for the genotoxicity of TCA based on a recent study reporting it caused chromosomal aberrations *in vivo;* however, there is limited or no evidence for other genotoxicity endpoints. TCA was reported as non-mutagenic in almost all bacterial assays, both with and without exogenous metabolic activation (S9). Considering both *in vitro* and *in vivo* studies, findings for DNA strand breaks were mostly negative, and were mixed for micronucleus formation. Methodological concerns in the *in vitro* studies limited the interpretation of the

evidence for other endpoints. Table 2-1 summarizes the conclusions for each genotoxic endpoint across studies) and details of the study findings are discussed below (as cited in IARC [2014] TCA Monograph, pp. 413-437).

TCA was tested for mutation in bacterial systems by numerous investigators (see IARC 2014), 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 several *S. typhimurium* reverse mutation assays, using standard or special tester strains or protocols, nor in a lambda prophage assay in *E. coli* (IARC 2014). 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).

The acidity of TCA is an important consideration in evaluating *in vitro* test results. An earlier study by Nestmann *et al.* (1980) showed that TCA was mutagenic in *S. typhimurium* bacteria only when dissolved in DMSO; results were negative when water was used as the solvent. Their observations suggested that a short-lived mutagen was formed when the test compound TCA was dissolved in DMSO. In another experiment in the same study, the findings for mutagenicity were negative when water was used as the solvent. Decarboxylation of TCA in DMSO was described in a study by Laque and Ronneberg (1970) and showed a first order reaction that was rate-dependent on the concentration of DMSO and availability of trichloroacetate ion. A report of increased chromosomal aberrations in cultured human peripheral lymphocytes exposed to TCA was considered by the authors (MacKay *et al.* 1995) to be related to a treatment-induced reduction in pH, rather than due to direct genotoxic action of the TCA. Recent studies in cultured human peripheral blood lymphocytes exposed to TCA *in vitro* by Varshney *et al.* reported that TCA (0.3% DMSO in culture) increased micronucleus frequency (2013a) and chromosomal aberrations (2013b).

TCA also reportedly induced dose-related increases in DNA strand breaks as measured by the comet assay in human HepG2 liver carcinoma cells (Zhang *et al.* 2012) but not in CHO cells (Plewa *et al.* 2002, 2010); neither of these studies used DMSO as a solvent.

In vivo studies of TCA reported chromosomal aberrations in bone marrow cells of Swiss mice (Bhunya and Behera 1987) and chickens (Bhunya and Jena 1996). TCA induced micronucleus formation in the peripheral erythrocytes of newt larvae (Giller *et al.* 1997) and bone marrow erythrocytes of Swiss mice (Bhunya and Behera 1987) but not in C57BL/6JfBL10/Alpk mice (Mackay *et al.* 1995). Dose-dependent increases in DNA single-strand breaks were induced by TCA in studies in $B6C3F_1$ mouse liver (Nelson and Bull 1988, Nelson *et al.* 1989, Hassoun *et al.* 2010b) However, some subsequent studies by the same authors failed to confirm the original finding (Nelson *et al.* 1989) even in the presence of liver growth induction (Styles *et al.* 1991). In addition, oral treatment by TCA did not induce DNA single-strand breaks in liver or epithelial cells from the stomach or duodenum of $B6C3F_1$ mice, nor in F344 rats following a single treatment by oral gavage (Chang *et al.* 1992).

2.7.2 Trichloroethanol (TCOH)

TCOH was negative in all bacterial mutagenicity tests without exogenous metabolic activation S9 (IARC 2014), but it did increase mutant frequency in the presence of S9 at a dose > 2,500 µg/plate (Beland 1999). It also induced formation of micronuclei *in vitro* in cultured human peripheral lymphocytes (Varshney *et al.* 2013a) (see Table 2-1 for conclusions of the evidence across studies).

2.7.3 Dichloroacetic acid (DCA)

There is some evidence for genotoxicity of DCA. Overall results for DCA *in vitro* show some evidence for mutagenicity both *in vivo* and *in vitro* and for DNA strand breaks *in viv*o but *in vitro*. Mixed results were observed for chromosomal aberrations (*in vitro* only) and micronucleus induction (*in vitro* and *in vivo*). Table 2-1 summarizes the conclusions for each genotoxic endpoint across studies and details of the findings are discussed below (as cited in IARC (2014) DCA Monograph, pp. 368-375).

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 not mutagenic in all other strains or 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.

Results were conflicting for DCA-induced micronucleus formation *in vitro*; a significant increase in micronuclei was reported in human peripheral blood lymphocytes (Varshney *et al.* 2013a) but not in L5178Y/*Tk*+/- mouse lymphoma cells (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 several other cell types, including 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 (Leavitt *et al.* 1997). 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; studies were negative in rat and newt larvae peripheral erythrocytes. However, two other studies reported negative results for micronuclei in bone-marrow erythrocytes of male and female Sprague-Dawley rats (Fox *et al.* 1996) and newt larvae peripheral erythrocytes (Giller *et al.* 1997). There is evidence that DCA induces single-strand breaks. Nelson and Bull (1988) and Nelson *et al.* (1989) reported increased DNA strand breaks in livers of $B6C3F_1$ mice and Sprague-Dawley rats exposed to

DCA orally. DNA strand breaks, alkali-labile sites, and crosslinking were also induced in blood leukocytes of male $B6C3F_1$ mice treated in drinking water (Fuscoe *et al.* 1996). However, there was no evidence of DNA strand breaks in the liver of male F344 rats, nor in the liver, spleen, or intestinal epithelium of male $B6C3F_1$ mouse after oral or drinking-water treatment with DCA (Chang *et al.* 1992). Study results on DCA induction of micronuclei were also somewhat conflicting.

2.7.4 Chloral hydrate (CH)

In vitro tests showed CH to be a direct mutagen and genotoxic for most of the endpoints tested, including the induction of DNA damage, chromosomal aberrations, and micronuclei. In other assays, CH caused non-disjunction and aneuploidy/polyploidy as well as transformed cells. A limited number of studies were conducted *in vivo*, and test results for many of these were inconsistent although there was some evidence suggesting that CH causes micronuclei (similar to the *in vitro* studies) in mouse bone marrow erythrocytes and spermatids, and mixed findings for DNA strand breaks, aneuploidy, and hyperploidy. Table 2-1 summaries the conclusions for each genotoxic endpoint across studies, and details of the findings are described below (as cited in IARC [2014] CH Monograph, pp. 452-462).

In several experiments in bacteria, CH exposure induced mutants in *Salmonella* tester strains TA100 and TA104, both with and without S9 metabolic activation; results in other strains were negative. Different tester strains of *Salmonella* are designed to detect different types of mutagenicity; positive results in TA100 are attributed to base-pair substitution so the overall response is considered positive for mutation. In the fungi *Aspergillus nidulans*, CH exposure caused aneuploidy and nondisjunction but not mitotic crossover (Crebelli *et al.* 1991, Käfer 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). There were no increases in mutations in L5178Y/$TK^{\pm}$-3.7.2C cells (Liviac *et al.* 2011).

In vitro exposure to CH in mammalian cells, both with and without S9, resulted in increased SCEs and chromosomal aberrations. It also induced micronuclei and aneuploidy, as well as cell transformation in Syrian hamster cells (IARC 2014). Several studies reported positive results for micronucleus formation; 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). Only one study evaluated micronucleus formation with the addition of exogenous metabolic activation S9; in that study, micronuclei were induced in lymphocytes in the absence, but not presence, of S9. 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). 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.* 2011).

Three studies reported that CH caused aneuploidy induction without exogenous metabolic activation in Chinese hamster cells; one study in mouse lymphoma cells reported it negative. CH exposure did not cause the formation of DNA-protein crosslinks in rat liver nuclei nor induce DNA single-strand breaks in rat primary hepatocytes (Keller and Heck 1988, Chang *et al.* 1992). A few studies have examined DNA binding of CH and adduct formation in CH-exposed tissues

and DNA. Keller and Heck (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. Other studies 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).

There are a few *in vitro* studies of CH exposure in human cells. DNA single-strand breaks were induced after CH exposure *in vitro* in human lymphoblast TK6 cells (Liviac *et al.* 2010), but not HepG2 cells (Zhang *et al.* 2012), as measured by the comet assay.

Results of *in vivo* studies of genotoxicity following exposure to CH were limited by few studies for some endpoints and somewhat 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 exposure (i.p.) in mouse strains C57B1, B6C3F$_1$, and BALB/c (early spermatids only) resulted in increased frequency of micronucleus formation in spermatids (Allen *et al.* 1994, Nutley *et al.* 1996, Russo and Levis 1992). Studies of micronucleus induction in bone-marrow erythrocytes reported positive effects in several strains of male mice, but not others. Positive results were reported for BALB/c, Swiss CD-1 and B6C3F$_1$ mice (Russo and Levis 1992, Russo 1992, Marrazzini *et al.* 1994, Beland 1999) but not NMRI (Leuschner and Leuschner 1991) or (C57BL/Cne x C3H/Cne)F$_1$ mice (Leopardi *et al.* 1993). Results were negative for micronucleus induction in BALB/c mouse peripheral blood lymphocytes (Graw**é** *et al.* 1997).

Significant increases in both micronuclei and SCE frequencies in peripheral blood lymphocytes from human infants were found following administration of CH as a sedative prior to a hearing test (Ikbal *et al.* 2004). CH induced chromosomal aberrations in sperm cells in one study (Russo *et al.* 1984), but was negative for other studies (IARC 2014). Aneuploidy was observed after exposure by i.p. injection in one of two studies in mouse secondary spermatocytes (Miller and Adler 1992, Leopardi *et al.* 1993) and hyperploidy, but not polyploidy, was reported for mouse bone-marrow erythrocytes (Marrazzini *et al.* 1994, Xu and Adler 1990).

2.7.5 *S*-(1,2-dichlorovinyl)-L-cysteine (DCVC), *S*-(1,2-dichlorovinyl)glutathione (DCVG), and NAcDCVC

The available studies on GSH-conjugation pathway metabolites of trichloroethylene suggested that they are genotoxic, however, there are few *in vivo* studies. More genotoxicity studies were available for DCVC than for DCVG or NAcDCVC. Almost all of the genotoxic endpoints evaluated *in vitro* were positive for DCVC, including mutation, DNA strand breaks, UDS (DNA repair), cell transformation, gene expression, and DNA and protein binding. Tests for micronucleus induction were negative. *In vivo* studies were limited to two endpoints, DNA strand breaks and protein binding, but both were positive. Table 2-1 summaries the conclusions of the evidence for each genotoxic endpoint and details of the findings are discussed below (as cited in IARC [2014] TCE Monograph, pp. 145-149).

DCVC and DCVG are cysteine intermediates of trichloroethylene formed during metabolic conjugation by glutathione-S-transferase; NAcDCVC has also been identified as another metabolites of trichloroethylene. DCVC has consistently shown genotoxic effects but there are very few studies on the genotoxicity of DCVG or NAcDCVC (IARC 2014).

Both DCVC and DCVG were positive for mutation induction in bacterial assays; both metabolites 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 (S9) (Vamvakas *et al.* 1988a, Dekant *et al.* 1986). Additionally, this response was diminished by addition of a beta-lyase inhibitor, suggesting that beta-lyase bioactivation plays a role in the genotoxicity (IARC 2014, Irving and Elfarra 2013). DCVC induced DNA strand breaks in male rabbit in perfused kidneys and proximal tubules, both *in vivo* and *in vitro* (Jaffe *et al.* 1985). Clay *et al.* (2008) observed a significant increase in DNA strand breaks two hours after a single oral dose of trichloroethylene (purity 99.5%) but reported no effect 16 hours after treatment.

In vitro exposure to DCVC resulted in increased UDS in Syrian hamster embryo fibroblasts and in a porcine kidney epithelial cell line (Vamvakas *et al.* 1988b, 1989) and cell transformation in rat kidney epithelial cells (Vamvakas *et al.* 1996, Mally *et al.* 2006). Gene expression was also increased in a kidney tubular epithelial cell line after treatment with DCVC (Vamvakas *et al.* 1996). Studies have shown that DCVC forms covalent adducts *in vitro* with DNA (Muller *et al.* 1998) and protein adducts *in vitro* and *in vivo*, (Hayden *et al.* 1992, Eyre *et al.* 1995). NAcDCVC was a direct-acting mutagen in a study in *S. typhimurium* strain TA2638; the effects were enhanced when kidney metabolic activation was included (Vamvakas *et al.* 1987).

2.8 Summary of genotoxicity and related effects of trichloroethylene and its metabolites

A table of summary assessments of the genotoxicity studies for trichloroethylene and its metabolites (primarily from authoritative reviews by IARC (2014) and EPA (2011a) and as discussed in this document) is provided in Table 2-1. The assessment for each endpoint in the table takes into account all of the information currently available, including consideration of any methodological and/or purity issues, to provide an overall evaluation. For example, positive findings for trichloroethylene might have been due to impurities or chemical stabilizers present in the test sample. Other issues considered that might have caused mixed findings are the use of DMSO as a solvent; whether trichloroethylene, which is a volatile liquid, was tested in liquid solution or in the vapor phase; and the metabolic activation system used in the assay.

2.8.1 Trichloroethylene

Overall, there is some evidence that trichloroethylene is genotoxic, which is likely caused by its metabolites. Some of these metabolites have been shown to be direct mutagens (see Section 2.8.2). In most *in vitro* studies of rodent and human cells and in *in vivo* studies, exposure to trichloroethylene caused DNA strand breaks and micronuclei formation. Importantly, trichloroethylene was shown to cause some types of genotoxicity in kidney cells or tissue from exposed animals. It also increased SCE in studies *in vitro* but not *in vivo*. There is little evidence that trichloroethylene is a direct mutagen; however, there is some evidence that trichloroethylene is mutagenic in bacteria (strain TA100, which detects base-pairing changes) and in yeast in the presence of metabolic activation. Evidence in other bacteria strains was weak and most positive findings in other bacteria strains were only observed in the presence of mutagenic stabilizers. Findings for mutagenicity in mammalian cells were mixed (based on only two studies) and negative in *in vivo* rodent studies. *In vivo* studies in rodents evaluating chromosomal aberrations, increased sister chromatid exchange, and UDS were negative.

Although not necessarily a genotoxic effect, trichloroethylene was reported to covalently bind mammalian DNA and protein from several tissues in rodents and humans in most *in vitro* and *in*

vivo studies. Binding to DNA and protein was enhanced by metabolic activation. Trichloroethylene also was shown to transform cells. DNA and protein binding and cell transformation were included in this section as relevant effects; however, positive results do not necessarily imply that the test agent is genotoxic. Cell transformation assays measure the phenotypic conversion from normal to malignant characteristics in mammalian cells and are capable of detecting both genotoxic and non-genotoxic carcinogens.

Trichloroethylene is highly metabolized, and trichloroethylene metabolites, as previously noted, 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 cell lines, and induced and uninduced primary cells from liver, kidney, blood, and embryos. Mixed results may be a consequence of incomplete metabolic activation in some of the systems used. Moreover, in a few cases, a requirement for metabolic activation was not observed, as trichloroethylene induced micronuclei and sister chromatid exchange (SCE) in cultured Chinese hamster ovary (CHO) cells without the addition of exogenous activation.

Another possible source to consider for confounding results is the use of solvents such as DMSO to solubilize the test chemical for treatment. Since trichloroethylene is not very water soluble, some *in vitro* assays (discussed above) utilized DMSO as the test chemical solvent; however, none of the *in vivo* assays identified reported using DMSO as a vehicle control. As discussed for the trichloroethylene metabolite TCA, there is a concern for pH effects when using solvents such as DMSO to prepare the test chemical. However, the reaction rate was dependent on the concentration of DMSO; the reaction-rate constants increased by a factor of 6 to 7 with a change in DMSO concentration from 50 to 86%. When trichloroethylene is tested *in vitro* with metabolic activation, either endogenous (e.g., primary cells) or exogenous (addition of S9), it can be metabolized to TCA. However, DMSO can be ruled out as an alternative explanation for explaining the positive findings of trichloroethylene. DMSO was not used as a solvent in the majority of the genotoxicity studies reporting positive finding. In the few studies where it was used (e.g., two *in vitro* studies in mammalian cells and in some studies in bacteria), positive findings for the specific endpoint (e.g., mutagenicity) were also found in studies not using DMSO as a solvent. Moreover, the DMSO used was usually at 0.3% to 1% final volume; only one study exceeded that at 2%, and thus it is unlikely that the few positive findings were due to DMSO interacting with the trichloroethylene metabolite, TCA, and some studies using DMSO as a solvent were negative. Finally, the other trichloroethylene metabolites are more likely to contribute to trichloroethylene genotoxicity, and no evidence was identified to suggest that they would interact with DMSO to cause a false positive.

2.8.2 Trichloroethylene metabolites

Metabolites of trichloroethylene resulting from both the GSH conjugation and oxidative pathways have been shown to induce genotoxic effects. The strongest evidence for genotoxicity is for DCVC and DCVG, followed by CH. There is some evidence for the genotoxicity of DCA and weak evidence for TCA. The GSH conjugation pathway 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 (with and without metabolic activation); notably there was an increased mutagenic response with the addition of kidney-derived microsomal metabolic activation. *In vitro*, DCVC induced UDS, and increased cell transformation in a variety of cell types, including rodent kidney cells; DCVC induced DNA strand breaks both *in vitro* and *in vivo* and showed protein

binding. The evidence is not strong for genotoxicity for the oxidative metabolites (CH, DCA, TCA TCOH) and there are only a few available studies for some. The most active metabolite of these is CH, 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 there was limited evidence that it induced DNA strand breaks and micronuclei, and possibly chromosomal aberrations. TCA is the least genotoxic metabolite; it was not mutagenic, the results *in vitro* may have been a pH-effect and/or due to the use of DMSO as a solvent. Results *in vivo* were mixed except for increases in chromosomal aberrations

Table 2-1. Summary assessment of genotoxicity and related effects for trichloroethylene and its metabolites

Summary calls for all of the endpoints in this table were determined by integrating the findings across all available studies, with consideration of methodological and/or purity issues. Summary calls include: positive +, mostly positive evidence (+), mixed results ±, mostly negative evidence (–) and negative –.

TCE or Metabolite Endpoint	Summary of findings across studies		
	In vitro		*In vivo* (animal)
	(–S9)	(+S9)	
TCE			
Gene mutation (bacteria and yeast)	–	(+)	NR
Gene mutation (mammalian)	–	± [a]	–
Gene conversion	–	(+)	NT
Aneuploidy	+	(+)	NT
Recombination/gene crossover	–	(+)	NT
DNA strand break	+	NT	(+)
UDS (DNA repair)	(–)	NT	–
Chromosomal aberrations	–	–	–
Sister chromatid exchange	+	(+)	–
Micronucleus induction	+	NT	(+)
DNA binding	±	+	(+)
Protein binding	+	NT	+
TCA			
Gene mutation	–	(–)	NT
DNA damage/strand breaks	(–)	NT	(–)
Chromosomal aberrations	(?) [b]	NT	+
Micronucleus induction	(+) [c]	NT	±
TCOH			
Gene mutation	–	+	NT
Micronucleus induction	+	NT	NT
DCA			
Gene mutation	(+)	(+)	+
Aneuploidy	–	NT	NT
DNA strand break	–	–	(+)
Chromosomal aberrations	±	NT	NT
Micronucleus induction	±	NT	±
CH			
Gene mutation	+	+	NT

TCE or Metabolite Endpoint	Summary of findings across studies		
	In vitro		*In vivo* (animal)
	(–S9)	(+S9)	
Non-disjunction	+	NT	NT
Aneuploidy/polyploidy	+	NT	±
Gene crossover	–	NT	NT
DNA strand break (liver)	–	NT	±
DNA damage (human lymphoblast)	+	NT	NT
Chromosomal aberrations	+	+	(–)
Sister chromatid exchange	+	+	NT
Micronucleus induction	(+)	–	(+)
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	+
NAcDCVC			
Gene mutation	+	+	NT

Sources: IARC (2014) and EPA (2011a), also Tabrez and Ahmad (2012), Varshney *et al.* (2013a,b), and Zhang *et al.* (2012), as described in the text; NT = Not tested.

[a]Bacteria results are based on positive findings in TA 100 studies not using stabilizers.

[b]Methodological concerns limit interpretation of the evidence across studies and positive findings may be due to a pH effect.

[c]Based on one study using 0.3% DMSO (See text).

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

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3 Human Cancer Studies

Introduction

As discussed in the "Background and Methods" section, the cancer hazard evaluation of trichloroethylene focuses on three specific cancers: kidney (see Section 4.1), NHL and its histological subtypes (see Section 5.1) and related cancers, and liver (see Section 6.1). 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, http://ntp.niehs.nih.gov/NTP/roc/thirteenth/Protocols/TCE_Protocol12-31-13_508.pdf).
2. Description of the study methods and characteristics and evaluation of study quality and other elements related to the utility of the studies to inform the cancer hazard evaluation: 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 (NAS 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 organized by descending publication date.

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. The largest 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. Three cohort studies reported on cancer findings among workers who had urinary trichloroacetic acid (U-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 third 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.

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. Among the three cohort studies of U.S. aircraft manufacturing workers with potential exposure to trichloroethylene, two cohort studies reported mortality findings (Lipworth *et al.* 2011, Morgan *et al.* 1998) and the third (Blair *et al.* 1998/Radican *et al.* 2008) reported both incidence and mortality. 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 nested case-control study by Yiin *et al.* (2009) of multiple myeloma evaluated trichloroethylene as a potential confounder for uranium exposure, which was the major focus of the study. 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 Exposure metric	Cancer assessment endpoints[a]
Nordic studies			
Vlaanderen *et al.* 2013	NOCCA study Population-based cancer registry and occupational database linkage Kidney (N = 76,130), liver (N = 896), NHL (N = 69,254), MM (N = 35,534)	Linkage of historical job information from census with national JEMs constructed from occupation data Cumulative exposure (incorporates exposure prevalence)	Incidence Internal analysis Kidney, liver, NHL, MN
Hansen *et al.* 2013	Pooled Nordic biomonitored cohort: diverse occupations N = 5,553 workers	Urine TCA surveillance U-TCA (mg/L)	Incidence External and internal analyses Kidney, liver, NHL, MM
Raaschou-Nielsen *et al.* 2003	Danish TCE-exposed blue-collar workers cohort: diverse occupations N = 40,049	Blue-collar workers in TCE-using companies with potential exposure to TCE Employment duration Year of first employment (crude surrogate for exposure level)	Incidence External analysis Kidney, liver, NHL, MM
Aerospace and aircraft manufacturing workers			
Lipworth *et al.* 2011	Burbank California (USA) aircraft manufacturing workers cohort N = 5,443	Qualitative JEM Employment duration	Mortality External and internal analyses Kidney, liver, NHL, MM
Radican *et al.* 2008/Blair *et al.* 1998	Utah (USA) aircraft maintenance workers cohort N = 7,204	Semi-quantitative JEM Cumulative exposure (units/yr) Exposure pattern (continuous, intermittent, peaks)	Mortality (Radican)/ incidence (Blair) External and internal analyses Kidney, liver, NHL, MM
Boice *et al.* 2006 (overlaps with Zhao *et al.* 2005)	Los Angeles (USA) rocket engine testing workers cohort N = 1,111	Qualitative JEM Ever exposure Exposure duration (kidney only)	Mortality External and internal analyses Kidney, liver, NHL, MM, CLL

Reference	Population	Exposure assessment Exposure metric	Cancer assessment endpoints[a]
Zhao *et al.* 2005 (overlaps with Boice *et al.* 2006)	Los Angeles (USA) aerospace workers cohort N = 6,044	Semi-quantitative JEM Cumulative exposure score	Mortality/incidence External and internal analyses Kidney, liver, NHL + leukemia combined
Morgan *et al.* 1998	Arizona (USA) aircraft manufacturing workers cohort N = 4,733	Semi-quantitative JEM Cumulative exposure score	Mortality External and internal analyses NHL, kidney, liver
Other studies of specific industries			
Silver *et al.* 2014	New York (USA) micro-electronics manufacturing cohort N = 34,494	Department-year exposure matrix Cumulative exposure ranking	Mortality Internal analyses Kidney, NHL, multiple myeloma, liver, biliary and gallbladder combined
Bahr *et al.* 2011	Kentucky (USA) uranium enrichment workers cohort N = 4,792	JEM Exposure level (ranked order)	Mortality External and internal analyses NHL, liver
Yiin *et al.* 2009	Tennessee (USA) nested case-control study of uranium enrichment workers N = 47,941 cohort 98 MM cases, 483 controls	Modified semi-quantitative JEM TCE evaluated as a potential confounder; major focus: uranium exposure Average cumulative exposure score	Mortality Internal anaylsis MM
Ritz 1999	Ohio (USA) uranium processing workers cohort N = 3,184	Semi-quantitative JEM Exposure level (low, moderate) Exposure duration	Mortality Internal analyses Liver
Henschler *et al.* 1995	German cardboard manufacturers cohort N = 169	Job location from individual work histories and knowledge of plant conditions. Ever exposed	Incidence External and internal analyses Kidney

Reference	Population	Exposure assessment Exposure metric	Cancer assessment endpoints[a]
Greenland *et al.* 1994	Massachusetts (USA) nested case-control study of electrical manufacturers cohort N = 1,821 cohort; 512 cancer deaths; 1,202 non-cancer deaths (controls)	Qualitative JEM Ever exposed	Mortality Kidney (N = 12), liver (N = 9), lymphoma (N = 15)
Wilcosky *et al.* 1984	Ohio (USA) nested case-control study of rubber manufacturing workers cohort N = 6,678 cohort (controls 20% sampling)	Working in area of authorized use of specific solvents Ever exposed (potential)	Mortality NHL (N = 9)
Environmental exposure			
Bove *et al.* 2014	North Carolina (USA) military cohort Drinking water study N = 154,932	Duration of residence and modeled TCE concentration in drinking water and cumulative exposure TCE (µg/L-month)	Mortality External and internal analyses 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 elements related to the utility of the studies to inform the cancer hazard evaluation

This section discusses the assessment of study quality and other elements related to the utility of the individual studies to inform the cancer hazard evaluation. Each study was assessed (prior to evaluating the findings) for the potential for biases and other factors related to informing the cancer hazard evaluation according to the approach described in the protocol. (See Appendix D, Tables D-4a,b for a study-by-study assessment of potential for biases, study quality, and study sensitivity.) The impact 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, Vlaanderen *et al.* 2013 Radican *et al.* 2008/Blair *et al.* 1998, Wilcosky *et al.* 1984, Zhao *et al.* 2005). There was the potential for bias 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, NAS 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) and the study of cardboard manufacturing workers (Henschler *et al.* 1995). A healthy worker effect would bias the findings of an external analysis towards the null. The study by Silver *et al.* only conducted internal analyses. 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.

There was generally insufficient information to evaluate the possibility of systematic selection out of the cohorts once established with the possible exception of Bahr *et al.* (2011) as noted above. 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 quality of job-exposure matrices and similar methods of estimating exposure varies considerably; for example, generic JEMs based on broad occupational or industry classifications (e.g. occupational titles or standardized industrial classification codes) may be insufficiently detailed for specific workplaces, jobs or tasks compared with those developed specifically for the study and validated or reviewed using, for example, expert assessment or veteran workers.

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. Cumulative exposure was characterized as the 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 the lack of detailed occupational information (tasks and working conditions), heterogeneity of exposure levels within and across jobs with the same job title, and overtime.

The pooled and updated Nordic study of Hansen *et al.* (2013) was based on biomonitoring data from urinary 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, and the half-life of U-TCA is ~100 hours, 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 in exposure classification for the analyses of a subcohort considered to have higher exposure than for the entire cohort.

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; no data were reported for exposure intensity or cumulative exposure.

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 1999, Yiin *et al.* 2009) 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 (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 Hansen *et al.* 2013, Henschler *et al.* 1995, Raaschou-Nielsen *et al.* 2003, Blair *et al.* 1998, Vlaanderen *et al.* 2013, and Zhao *et al.* 2005. Mortality-only analyses include the cohorts by Bove *et al.* 2014, Bahr *et al.* 2011, Boice *et al.* 2006, Greenland *et al.* 1994, Lipworth *et al.* 2011, Morgan *et al.* 1998, Radican *et al.* 2008, Ritz 1999, Silver *et al.* 2014, and Yiin *et al.* 2009. Disease misclassification was unlikely for kidney cancers (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. Disease assessment 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 disease ascertainment of the Kentucky uranium enrichment workers (Bahr *et al.* 2011) could not be evaluated because of inadequate information on the source and completeness of vital status and cause of death data.

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, were 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 were 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 are the most informative for the classification of NHL and its subtypes. The ICD-7 NHL classifications used in the Nordic studies (Raaschou-Nielsen *et al.* 2003, Hansen *et al.* 2013, Vlaanderen *et al.* 2013) and to a lesser extent 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 somewhat broader and less informative than more recent systems, which were applied in only two studies (Zhao *et al.* 2005, Radican *et al.* 2008).

Finally, 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 (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), and the length of follow-up, which is of particular concern for longer latency cancers such as liver and kidney cancer. True relative risks will usually be lower among

study populations with lower exposure (NAS 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, NAS 2006 for some of these studies) for ever vs. never exposed analyses, and 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. Most studies may not have had sufficient power to detect lower risk estimates (e.g., 1.3) for ever vs. never exposure. Some studies did not report the number of trichloroethylene-exposed cases for the cancer sites of interest (Yiin *et al.* 2009, Silver *et al.* 2014).

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. Moreover, different studies used different exposure metrics (see Table 3.1), which complicates comparisons of exposure levels across studies. 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 ppm 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 from Dr. Patricia Stewart to Dr. Ruth Lunn [June 23, 2014]). The National Academy of Sciences (NAS 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 especially in the earlier time periods (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 (Silver *et al.* 2014, Fleming *et al.* 2014, Yiin *et al.* 2009). In other studies, exposure level (Ritz 1999), probability (Wilcosky *et al.* 1984), or few workers appear to be exposed to trichloroethylene by indirect means (Greenland *et al.* 1994). With respect to the drinking water study (Bove *et al.* 2014), the authors estimated that maximum consumption could be 3.6 mg/day from water, based on measured trichloroethylene levels (combining ingestion, dermal, and inhalation exposure from showering), 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-year. 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 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 1999, Boice *et al.* 2006, Vlaanderen *et al.* 2013), (4) adequacy of the exposure surrogate for evaluating exposure 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.

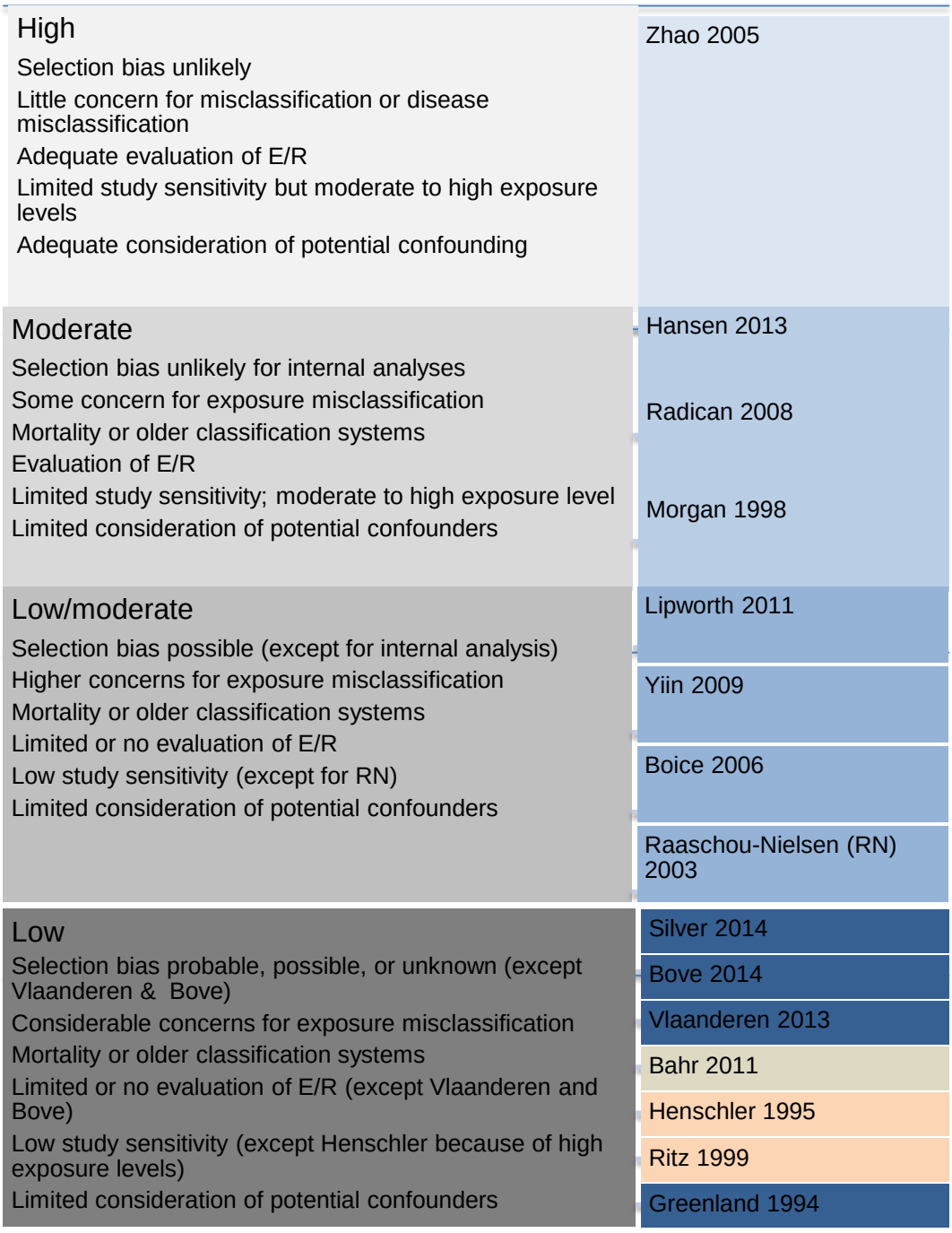
3.2.2.6 Summary

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 overall utility of the studies, including potential for biases and study sensitivity. The most informative studies (moderate- or high-utility 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, 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 ability to inform the cancer hazard evaluation, 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 aircraft 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. In the Nordic study of blue-collar workers, there was the potential for confounding by, e.g., smoking due to the differences in socioeconomic status between the cohort and the referent population; potential residual confounding from radiation exposure was also considered possible in the study by Yiin *et al.* (2009). Overall, however, the other limitations in all the studies (e.g., study sensitivity) were primarily 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.* 1994) were considered to be of limited ability to inform the cancer hazard evaluation primarily because of low study sensitivity (e.g., lower levels of exposure) or potential for exposure misclassification. 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 have inadequate utility and was not brought forward in the hazard evaluations for specific cancers (Sections 4, 5, and 6).

Figure 3-1. Study utility ranking: Cohort studies



E/R = exposure response.
Grey: Utility to inform hazard evaluation; light grey – highest. Blue: Overall potential biases towards the null or lower sensitivity; light blue: most sensitive or least biased. Peach: Most potential biases away from the null. Tan: Multiple limitations; overall direction of potential biases is unknown.

3.3 Kidney or liver cancer case-control studies

3.3.1 Overview of the methodologies and study characteristics

Table 3.2 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. 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). 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. 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). 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. 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, Table D-1, 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 Exposure metric	Cancer assessment
Studies in specific areas with knowledge of local industries			
Moore *et al.* 2010	Multi-center, Central and Eastern Europe, hospital-based 1,097/1,476	In-person interview using structured questionnaire, expert assessment Exposure duration (years, hours) Cumulative exposure (ppm-yr) Average exposure (ppm)	Incident RCC cases
Charbotel *et al.* 2006, 2009	Arve Valley, France, hospital-based 86/326	Telephone interview using structured questionnaire, expert assessment, semi-quantitative JEM Cumulative exposure (ranked)	Incident and deceased RCC cases
Brüning *et al.* 2003	Arnsberg, Germany, hospital-based 134/401	In-person or proxy interview using structured questionnaire, self- and expert assessment (JEM) Exposure + narcotic symptoms Exposure duration (yr) Longest job using TCE, metal degreasing	Incident and deceased RCC cases
Vamvakas *et al.* 1998	Arnsberg, Germany, hospital-based 58/84	In-person (case or proxy) interview using structured questionnaire, expert assessment Ever exposed Exposure category (ranked)	Incident and deceased RCC cases
Other studies			
Christensen *et al.* 2013	Montreal, Quebec (Canada), hospital- and population-based 177/533	In-person interview using structured questionnaire, expert assessment Ever and substantial exposure (includes probability)	Incident RCC and liver cancer cases
Pesch *et al.* 2000a	Multi-center, Germany, population-based 935/4,298	In-person interview using structured questionnaire, expert assessment, JTEM Median, high & substantial exposure (includes probability)	Incident RCC cases

Primary reference	Study Population Total # Cases/controls	Exposure assessment Exposure metric	Cancer assessment
Dosemeci *et al.* 1999	Minnesota, (USA) population-based 438/687	In-person interview using structured questionnaire (occupation, exposures), JEM Ever exposed	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 elements related to the utility of the studies to inform the cancer hazard evaluation

The methods for evaluation of study quality and other relevant study elements of the kidney and liver cancer case-control studies were 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.

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 from 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.

Similar to many case-control studies, participation rates were somewhat higher among cases (greater than 80%) than 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), the Montreal study (Christensen *et al.* 2013), and the multi-center European study (Moore *et al.* 2010) were considered to have high-quality assessments because they collected detailed information on job tasks, considered calendar year and personal protective equipment, 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. 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) studies 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 possible 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 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 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., the ability to detect an effect) is a function of exposure prevalence and levels, sample size and length of follow-up. 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. Moreover, different metrics were used in the different studies, which complicates comparisons of exposure levels across studies (see Table 3-2). 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, NAS 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 NAS (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 French (Charbotel *et al.* 2006, 2009) and German (Brüning *et al.* 2003, Vamvakas *et al.* 1998) studies conducted in small industrial areas had adequate sensitivity to detect an effect (if true) 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 Eastern and Central European study (Moore *et al.* 2010) had adequate study sensitivity due to its large size and estimated moderate exposure (among the highest exposed subjects), 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 (surrogates 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.* (2000a) 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 use of 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 ability 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 utility. 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 and other elements related to its utility to inform the cancer evaluation,

discuss whether chance, bias, or confounding can be ruled out for studies with positive findings, discuss other studies 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.* 2013), 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., 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.* 2013) and the Montreal, Quebec study (Christensen *et al.* 2013). The InterLymph 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 Exposure metric	Cancer assessment
Christensen *et al.* 2013 1979–1985	Montreal, Quebec Canada 215/533	In-person interview using structured questionnaire, expert assessment Ever and substantial exposure (includes probability)	NHL, MM ICD-9: 200+202 (NHL) Hospital; histologically confirmed
Cocco *et al.* 2013 1991–2004	4 pooled studies (Cocco *et al.* 2010, Purdue *et al.* 2011a, Miligi *et al.* 2006, Orsi *et al.* 2010) 3,788/4,279	Questionnaire, expert assessment Exposure probability Exposure duration (yrs) Exposure frequency (% work time) Exposure intensity (ppm)	NHL and subtypes WHO InterLymph consortium classification Histologically confirmed
Deng *et al.* 2013/Wang *et al.* 2009a 1996–2000	Connecticut (USA) 601/7,171	Questionnaire, JEM Exposure probability Exposure intensity (ranked)	NHL and subtypes ICD-O-2, codes M-9590–9642, 9690–9701, 9740–9750 Histologically confirmed
Gold *et al.* 2011 2000–2002	SEER registries, Seattle Detroit 9,731/9,732	In-person interview using structured questionnaire, expert assessment Exposure duration (yrs) Cumulative exposure (ppm-hrs)	MM ICD-O-2/3 SEER cancer registry; histologically confirmed
Costantini *et al.* 2008 1991–1993	Regional Italy 263/1,100 MM 586/1,278 (all leukemia; subtype totals NR)	In-person interview using structured questionnaire, expert assessment Exposure intensity (ranked) Exposure duration (yr)	MM, CL ICD-9: 203 (MM), 204.1 (CLL) Hospitals; histological confirmation NR
Persson and Fredrikson 1999 1964–1986	Sweden Pooled analysis of 2 studies (1983 and 1989) 199/479	Self-reported ranked exposure Ever exposed	NHL 2nd study: ICD-8: 200+202 NR in 1989 study Hospital; histologically confirmed
Nordström *et al.* 1998 1987–1992	Sweden 121/484	Self-reported occupational history Ever exposed	HCL Cancer registry; classification and histological confirmation NR
Hardell *et al.* 1994 1974–1978	Umeå Region Sweden	Self-reported occupational history Ever exposed	NHL Hospital histologically verified; Rappaport classification; stages and anatomical sites

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 elements related to the utility of the studies to inform the cancer hazard evaluation

The methods for evaluation of study quality of the NHL case-control studies were 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. Most studies had participation rates greater than 80% for cases and 70% for controls. The Swedish studies had high participation rates (less 10%) Studies having lower participation rates among cases and controls were the Connecticut population-based case-control study of NHL (Deng *et al.* 2013/Wang *et al.* 2009a), the SEER study (Seattle, Washington and Detroit Michigan) of multiple myeloma, and one of the component studies (Purdue *et al.* 2011a, Cocco *et al.* 2010 for population controls) of the pooled InterLymph case-control study (Cocco *et al.* 2013).

3.4.2.2 Information bias: Exposure assessment and misclassification

The exposure assessments in the InterLymph pooled case-control study (Cocco *et al.* 2013), the Montreal study (Christensen *et al.* 2013), the 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.* 2013) and Seattle 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.* (2011a), 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 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 and exposures to a specific set of chemicals with either a minimum (one day) criterion for the exposed group (Hardell *et al.* 1994 and Nordstrom *et al.* 1998) or five categories of ranked exposure with a minimum of 1 year of exposure (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. The direction of the bias is not known since self-reported data may differ by disease status; however, there is also the potential for non-differential misclassification.

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 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.* 2013), 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 (the ability to detect an effect from exposure) 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 cases (Appendix D, Table D-6b). Actual exposure levels were not reported for any studies. Some studies (Cocco *et al.* 2013, 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.* 2013) 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 study 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.* 2013), 7% of the workers were exposed to trichloroethylene, but only 1% were classified as definitely exposed. Two studies (Cocco *et al.* 2013, 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.* 2013, 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. In the study by Hardell *et al. (*1994), subjects may have been exposed to phenoxyacetic acids, chlorophenols or other organic solvents. None of the other studies adjusted for co-exposures in their analysis, although the InterLymph study (Cocco *et al.* 2013) 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.* 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. 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 utility 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 utility because of concerns for substantial misclassification of exposure (self-reported), use of older disease classification systems, and relatively small numbers of exposed subjects.

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 2007 to 2011 (SEER 2014a) were approximately 21.2 (male) and 10.6 (female) for incidence and 5.8 (male) and 2.6 (female) for mortality, with a five-year survival rate of ~70%, suggesting that incidence data may be more informative than mortality data. The incidence rate of kidney cancer has been increasing for several decades in the U.S. from an incidence rate of approximately 7 per 100,000 in 1975 at a rate of approximately 2% per year over the past decade, while death rates have declined slightly by approximately 0.6% per year. Incidence rates and trends in other European countries (Ferlay *et al.* 2013, 2014), in which the remainder of the studies were conducted, are broadly similar; for example, age-standardized incidence rates in the U.K. in 2011 (Cancer Research UK 2014a) were approximately 16 per 100,000 (male) and 9 (female), with a similar increase from an incidence rate approximately 5 per 100,000 at a rate of approximately 3% per year over the past decade. Latencies for solid tumors such as kidney cancer are generally estimated to exceed approximately 20 years, but may vary considerably. Incidence rates generally increase sharply after approximately 50 years of age. Case-control studies of trichloroethylene and kidney cancer are of renal-cell carcinoma, which make up approximately 90% of all kidney cancers, whereas most of the cohort studies are of combined (renal, pelvis and/or ureter) kidney cancer.

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, and other elements related to the ability to inform the cancer hazard assessment (such as study sensitivity) 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 the utility of the studies. Figure 4-1 (below) provides an overview of the conclusions from that evaluation and identifies the most informative studies based on the overall utility of the study.

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 studies may not be sensitive to detect effects that are due to high exposures. In addition, a major limitation of the studies was non-differential exposure misclassification, which would most likely bias the findings toward the null. The case-control study by Vamvakas *et al.* (1998) and the cohort study by Henschler *et al.* (1995) had methodological concerns that may potentially bias the findings away from the null.

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

Figure 4-1 Study utility ranking: Kidney cancer

High Selection bias unlikely (except Moore) Little concern for exposure or disease misclassification Adequate evaluation of E/R Adequate or good study sensitivity (limited for Zhao, but moderate to high exposure levels) Adequate consideration of potential confounders	Moore 2010 Charbotel 2006 Zhao 2005
Moderate Selection bias unlikely (except Brüning, Morgan*) Some concern for exposure misclassification (except Brüning) Mortality analysis (Radican, Morgan) Evaluation of E/R (limited for Brüning) Limited study sensitivity (except Brüning) Limited methods to consider potential confounding (except Brüning)	Hansen 2013 Radican 2008 Brüning 2003 Morgan 1998
Low/moderate Selection bias unlikely (except RN and Lipworth) Some concern for exposure misclassification Good outcome assessment (except Lipworth) Limited or no evaluation of E/R Lower study sensitivity (except RN) Limited methods to consider potential confounders (cohorts)	Raaschou-Nielsen (RN) 2003 Lipworth 2011 Pesch 2000 Christensen 2013 Dosemeci 1999
Low Selection bias a concern (Vamvakas, Henschler, Greenland) Considerable concerns for exposure misclassifcation (except Vamvakas, Henschler) Mortality (except Vamvakas) Limited or no evaluation of E/R (except Vlaanderen, Bove) Limited methods to consider potential confounding (except Vamvakas)	Silver 2014 Bove 2014 Vlaanderen 2013 Greenland 1994 Vamvakas 1998 Henschler 1995

Grey: Utility to inform the hazard evaluation; light grey – highest. Blue: Overall biases towards the null or lower sensitivity; light blue –most sensitive or least biased. Peach: Most, potential biases away from the null; Tan: Multiple methodological concerns: overall direction of potential biases unknown.
* Bias possible for external but not internal analyses.

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 the ability of the studies to inform the cancer hazard evaluation 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-cell car 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 highly informative 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 statistically 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, statistically non-significant 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 statistically non-significant 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 $\geq$ 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 NAS (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 less informative (i.e., lower utility to inform the cancer hazard evaluation) 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 the external but probably not the internal analyses). However, the NAS (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. Silver *et al.* (2014) reported a HR of 1.24 (95% CI = 0.87 to 1.77, 56 exposed deaths) among U.S. microelectronics workers; the cohort was relatively young, with only 17% deaths in the total cohort, and the exposure assessment was limited. 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. Finally, Bove *et al.* (2014) reported a HR of 1.52 (95% CI = 0.64 to 3.61, 11 exposed deaths) among U.S. 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; a significant increase in risk was observed among those with at least one active allele of the GSTT1 genotype but not among individuals with GSTT1-null 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, NAS 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. 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					
Vlaanderen *et al.* 2013	5 Nordic countries Record linkage of cancer registry with census questionnaire M: 44,708 cases, 223,540 controls F: 31,422 cases, 157,110 controls Semi-quantitative JEM	*Cumulative exposure (unit-years)* 0 0.04 0.13 0.72 *High-exposure group* <u>Cumulative</u> Men Women <u>Intensity × prevalence</u> Men Women		*HR (incidence*) 1.00 1.01 (0.95–1.07); 1,217 1.02 (0.97–1.08); 1,556 1.00 (0.95–1.07); 1,372 0.92 (0.77–1.09); 159 0.92 (0.77–1.09); 92 1.10 (0.97–1.25); 297 0.78 (0.62–0.97); 9	Low prevalence of exposure (TCE) and exposure levels likely to be low. Matching criteria: Age, country, sex Strengths: Long follow-up, large numbers of cases Limitations: Misclassification of exposure likely; JEM had poor sensitivity and did not account for heterogeneity within jobs and over time. *Null*: No evidence for a positive association but limited utility due to low exposure levels and exposure misclassification
Hansen 2013 (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 5,553 (3,776 M, 1,777 F) Biomonitoring (U-TCA)	*All exposed subjects* 0-yr lag 10-yr lag 20-yr lag *U-TCA (mg/L)* < 5 5–25 25–50 > 50 P_{trend}	*SIR* 1.01 (0.70–1.42); 32 1.04 (0.71–1.50); 30 1.11 (0.67–1.73); 19	 *HRR (no lag); incidence* 1.0 (Ref); 9 1.12 (0.46–2.70); 11 0.81 (0.21–2.97); 3 2.04 (0.81–5.17); 9 0.19	Low exposure levels for most workers (only 20% exposed to ≥ 20 ppm) and short duration of employment Covariates: Age, sex, calendar period, country; indirect consideration of smoking and alcohol consumption Strengths: Biomonitoring data; large numbers of workers ever

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
					exposed Limitations: Only 2 or 3 U-TCA measurements per individual and unlikely to estimate lifetime or cumulative exposure; low statistical power for evaluating modest risks; limited ability to evaluate exposure-response relationship *Limited evidence for a positive association*: Statistically non-significant, moderately elevated effect estimate in the highest exposed group
Raaschou-Nielsen 2003 (Potential overlap with Hansen 2013)	Danish blue-collar workers 40,049 M+F (approx. 70% M) Working at TCE company; size of company surrogate for TCE exposure prevalence	*Subcohort: higher exposed* <u>Lag time (yr)</u> 0–9 10–19 ≥ 20 <u>Duration employment (yr)</u> 1–4 ≥ 5 <u>Yr. of 1st employment</u> Before 1970 1970–1979	*SIR* 1.4 (1.0–1.8); 53 0.9 (0.3–1.8); 6 1.5 (0.9–2.2); 22 1.6 (1.0–2.3); 25 1.1 (0.7–1.7); 23 1.7 (1.1–2.4); 30 1.9 (1.4–2.6); 41 0.7 (0.4–1.2); 12		Higher levels of TCE prior to 1970 (40–60 ppm); low levels of exposure after that time. Covariates: Age, sex, calendar year Strengths: Large numbers of exposed cases; subcohort of subjects with higher exposure potential Limitations: Young cohort, possible selection bias for difference in SES, external analysis only; possible exposure misclassification *Evidence for a positive association*: Statistically

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
					significantly, moderated elevated effect estimates; some evidence for exposure-response relationship unlikely to be explained by confounding by smoking or differences in SES
Aerospace and aircraft workers					
Lipworth *et al.* 2011 (update of Boice *et al.* 1999)	Burbank, CA (USA) aircraft manufacturing workers 5443 (approx. 80% M) Qualitative JEM Individual work histories	TCE *TCE: years exposed* 0 < 1 1–4 5+ P_{trend}	*SMR* 0.66 (0.38–1.07); 16	*RR (mortality)* 1.00; 33 0.52 (0.21–1.30); 6 0.42 (0.13–1.42); 3 0.85 (0.33–2.19); 6 0.20	Exposure levels not reported; exposure duration likely to be short Covariates: Age, date of birth, date of hire, termination date, sex and race Strengths: Long follow up, adequate number of deaths for ever exposure 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 *Null:* No evidence for a positive association but limited utility (limitations are mainly towards the null)
Radican *et al.* 2008 (mortality to	Utah (USA) aircraft maintenance workers	*Mortality* *Ever-exposed (M & F)* 1990 follow-up		*HR (mortality)* 2.3 (0.6–8.4); 15	Estimated exposure: Most workers exposed to low levels (~10 ppm), modest number 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
2000) Blair *et al.* 1998 (incidence 1973–1990)	7,204 (6,153 M, 1,051 F) Semi-quantitative JEM Individual work histories	2000 follow-up Only 2 cases in females *Males only 2000 follow-up* Cumulative exp. (unit-yr) All 0–5 2–25 > 25 Exposure pattern Low intermittent Low continuous Peak infrequent Peak frequent *Incidence 1990 follow-up* Cumulative exp. (units-yr) None 0–5 2–25 > 25		1.18 (0.47–2.94); 18 1.24 (0.41–3.71); 16 1.87 (0.59–5.97); 10 0.31 (0.03–2.75); 1 1.16 (0.31–4.32); 5 1.58 (0.52– 4.76); 15 1.79 (0.57–5.62); 11 1.04 (0.19 –5.70); 2 1.11 (0.31–3.96); 6 *RR (incidence)* 1.6 (0.5–5.4); 9 1.4 (0.4–4.7); 9 1.3 (0.3–4.7); 5 0.4 (0.1–2.3); 2	workers exposed to higher levels (~100 ppm). Covariates: Age, calendar year race, and sex Strengths: Adequate semi-quantitative JEM, long follow-up, adequate statistical power for ever exposure Limitations: Potential for exposure misclassification because of missing information for some workers; limited power due to low numbers of higher exposed workers; long follow-up time (45 years) may be past induction time *Null:* Small increase in effect estimate but limited utility due to limited statistical power
Boice *et al.* 2006 (Overlaps with Zhao *et al.* 2005)	Los Angeles, CA (USA) Rocket engine testing workers 1,111 Men Qualitative JEM; Individual work histories	*Ever exposed* *Exposure to TCE during engine flush (test-yr)* Referent (other depts.) 0 < 4 ≥ 4 P_{trend}	*SMR* 2.22 (0.89–4.57); 7	*RR (mortality*) 1.00; 28 1.21 (0.33–4.35); 3 2.51 (0.27–23.5); 1 3.13 (0.74–13.2); 3 0.59	Exposure occurs during test engine flush, which is likely to be high. Covariates: Date of birth, year of hire, pay type (surrogate for SES) and exposure to hydrazine Strengths: Adequate follow-up Limitations: Qualitative exposure assessment; few exposed deaths *Limited evidence for a positive*

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
					association: Statistically non-significant elevated effect estimate among highest exposed group
Zhao *et al.* 2005 Overlap with Boice *et al.* 2006	Los Angeles, CA (USA) Male aerospace workers 6,044 (mortality) 5,049 (incidence) Semi-quantitative JEM; individual work history	All analyses: 3 levels TCE cumulative exposure score *Co-exp. Unadj.; 0-yr lag* Low Medium High P_{trend} *Co-exp. Adj.; 0-yr lag* Low Medium High P_{trend} Similar RR for 20-yr lag adj. model *Co-exp. Unadj. 0-yr lag* Low Medium High P_{trend} *Co-exp. Adj. 20-yr lag* Low Medium High P_{trend} No association in co-exp		*RR (*incidence) 1.00; 6 1.87 (0.56–6.20); 6 4.90 (1.23–19.6); 4 0.023 1.00; 6 1.26 (0.26–6.14); 6 7.71 (0.65–91.4); 4 0.103 *RR (mortality)* 1.0; 7 1.43 (0.49–4.16); 7 2.03 (0.50–8.32); 3 0.307 1.00; 10 1.69 (0.29–9.70); 6 1.82 (0.09–38.6); 1 0.635	Exposure levels not reported but presumed to be high. Covariates: All models – time since first employment, SES, age at event- additional analysis adjusted for co-exposure to carcinogenic chemicals. Strengths: Semi-quantitative exposure assessment; multivariate analysis evaluating exposure-response relationships adjusting for co-exposures Limitations: Few cases in subgroup analyses *Evidence for a positive association:* Statistically significant, high effect estimates; evidence of exposure-response relationship; unlikely to be explained by confounding by 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
		adj. 0-yr lag			
Morgan *et al.* 1998	Arizona (USA) Aircraft manufacturing workers 4,733 (2,555 M, 2,178 F) Semi-quantitative JEM; individual work history	All TCE-exposed workers Cumulative exp. score Low (2,357) High (2,376) Peak (med/high) vs. low/no	*SMR (All)* 1.32 (0.57–2.60); 8 0.47 (0.01–2.62); 1 1.78 (0.72–3.66); 7	*RR (mortality)* 1.14 (0.51–2.58) 8[b] 0.31 (0.04–2.36); 1 1.59 (0.68–3.71); 7 1.89 (0.85-4.23); 8	High-exposure jobs were considered to be ≥ 50 ppm Covariates: Age at hire, gender (decade of hire considered but no effect) Strengths: Long follow-up and semi-quantitative exposure Limitations: Evidence of a HWE; potential exposure misclassification among low/medium exposure groups; mortality analysis and few exposed deaths *Limited evidence for a positive association:* Statistically non-significant elevated effect estimate among the highest exposed group
Other occupational studies					
Silver *et al.* 2014	New York State (USA) micro-electronics manufacturing workers cohort mortality 3,113 TCE exposed Semi-qualitative JEM	5 modified exposure years (exposure duration modified by exposure potential); 10-yr lag		1.24 (0.87–1.77); NR	Exposure levels NR; only 13.9% of cohort exposed. Covariates: Paycode and sex, age, Variables considered in analyses but which did not change risk estimate were birth cohort, time since last exposure (healthy worker survival), hire era, and employment duration prior to 1966

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
					Limitations: Evidence of HWE, Exposure classification based on potential exposure and duration; only one cumulative exposure variable reported in analysis. Young cohort with only 17% deaths *Limited evidence for a positive association*: Non-statistically significant elevated effect estimate
Henschler *et al.* 1995	German cardboard manufacturing cohort 169 exposed men 190 unexposed men Individual work history	Rates 1956–1993 Denmark 1956–1993 German 1956–1992 Denmark 1956–1992 German rates Cases within follow-up Cases outside of follow-up	*SIR* 11.15 (4.49–23.00); 7 13.53 (5.44–27.89); 7 7.97 (2.59–8.59); 5 9.66 (3.14–22.55); 5	Mantel-Haenszel test 7.15 (NR); 7: $P = 0.005$ 5.35 (NR); 5: $P = 0.014$ (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). Covariates: Age Strengths: Detailed information on plant conditions with evidence of high exposure, misclassification unlikely Limitations: Possible selection bias (original cluster investigation) *Evidence for a positive association*: Statistically significant, high, elevated effect estimates: likely an overestimate of the risk estimate, however, unlikely that biases would nullify

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
					the association.
Greenland *et al.* 1994 (nested case-control)	Massachusetts (USA) electrical manufacturers N = 12 cases (exposed controls NR)	Ever exposure		*OR (cases)* 0.99 (0.30–3.32); NR	Only 10% of jobs had exposure to TCE, most of which were from indirect exposure. Covariates: Age, date of death, covariates that changed risk estimate by 20%. Limitations: Small numbers of cases and controls and short follow-up, possible selection bias, low quality exposure assessment *Null:* No evidence of an association but limited utility (limitations are mainly towards the null)
Environmental exposure					
Bove *et al.* 2014	North Carolina (USA) (Camp Lejeune) 154,932 men and women	TCE in drinking water (µg /L-month) < 1 (43%) > 1–3,100 (20%) > 3,100–7,700 (18%) > 7,700–39,745 (20%)		*HR (Mortality); 10 yr lag* 1.0; 13 1.54 (0.65–3.61); 11 1.21 (0.47–3.09); 8 1.52 (0.64–3.61); 11	Estimated mean levels (µg/L-month) TCE from water supply = 358.7; overall cumulative exposure = 6,369 (median) and 5,289 (mean); 20% were exposed to levels between 7,700 and 39,745 Covariates: sex, race, rank, 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

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
					Strengths: Large cohort and adequate modeling of exposure Limitations: Young cohort; no information on individual water consumption; potential confounding from other contaminants e.g., tetrachloroethylene *Limited evidence for a positive association*: Statistically non-significant elevated effect estimates

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,

[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				
Moore *et al.* 2010	Central/Eastern Europe Hospital based 1999–2003 1,097 cases RCC 1,476 hospital controls Expert assessment based on occupational data from interviews	*High confidence assessments* No TCE exposure Ever TCE exposure Years TCE Exposure < 13.5 ≥ 13.5 P_{trend} Hours TCE Exposure < 1,080 ≥ 1,080 P_{trend} Cumulative (ppm-yr) < 1.58 ≥ 1.58 P_{trend} Average intensity (ppm) < 0.076 ≥ 0.076 P_{trend} *TCE exposure stratified by GSTT1* *GSTT1 null* No Yes Duration (years) Hours Cumulative exposure	*OR* 1.00; 777/1144 2.05 (1.13–3.73); 29/19 1.89 (0.84–4.28); 15/10 2.25 (0.95–5.29); 14/9 0.02 1.22 (0.48–3.12); 9/9 2.86 (1.31–6.23); 20/10 0.01 1.77 (0.64–4.80); 9/7 2.23 (1.07–4.64); 20/12 0.02 1.73 (0.75–4.02); 13/10 2.41 (1.05–5.56); 16/9 0.02 1.0; 119/149 0.93 (0.35–2.44) P_{trend} 0.41 0.95 0.75	Intensity and prevalence of occupational exposure have been higher in central and eastern Europe than other industrial areas. Covariates: Age, sex, center; residence, smoking, BMI, and history of hypertension considered but did not affect risk estimate Strengths: Analysis of high confidence assessment reduces potential for exposure misclassification. Large number of exposed cases and controls in overall and subanalysis Limitations: Potential for selection bias. *Evidence for a positive association:* Statistically significant, moderately elevated effect estimates; evidence of exposure-response relationship; unlikely to be explained by biases or confounding. Increased risks of cancer among subjects with an active GSTT1 allele but not with GSTT1 null genotype is consistent with proposed mechanism of carcinogenicity

Reference	Study Size (N) Exposure assessment	Exposure groups	RR or OR (95% CI) # exposed cases/controls	Interpretation
		Average exposure *GSTT1 Active* No Yes Duration (years) Hours Cumulative exposure Average exposure	1.0 1.0; 466/729 1.88 (1.06–3.33); 23 P_{trend} 0.03 0.02 0.01 0.02	
Charbotel *et al.* 2006, 2009	Arve Valley, France 86 RCC cases 326 hospital controls Expert assessment, semi-quantitative JEM	*2006 analysis* Non-exposed (ever) Ever exposed *High confidence (Model 1)* Cumulative dose Non-exposed Low Medium High Cumulative exp. + peaks Non-exposed Low/medium no peaks Low/medium + peaks High no peaks High + peaks *All workers* High cum. dose (Model 1) High cum. dose (Model 2) High + peak (Model 1) High + peaks (Model 2) *2009 analysis: combined effects TCE & cutting oil (Model 2)*	*OR* 1.00; 44/188 1.88 (0.89–3.98); 16/37 1.00 0.85 (0.10–7.41); 1/8 1.03 (0.29–3.70); 4/13 3.34 (1.27–8.74); 11/16 1.00; 44/188 0.90 (0.27–3.01); 4/18 1.34 (0.13–14.02); 1/3 2.74 (0.66–11.42); 4/8 3.80 (1.27–11.40); 7/8 2.16 (1.02–4.60); 16/37 1.96 (0.71–5.37) 2.73 (1.06–7.07); 8/14 2.63 (0.79–8.83)	High intensity of exposure and high exposure prevalence. Screw cutting industry. Estimated TCE intensities for high exposure jobs were 300–600 ppm. 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 Strengths: Good exposure assessment and consideration of co-exposures. Limitations: Small number of exposed cases and controls in subgroup analyses *Evidence for a positive association* Statistically significant, moderately elevated effect estimates; evidence of exposure-response relationship; unlikely to be explained by

Reference	Study Size (N) Exposure assessment	Exposure groups	RR or OR (95% CI) # exposed cases/controls	Interpretation
		Cutting oil/TCE No/No Yes/No No/Yes Yes/< 50 ppm Yes/≥ 50 ppm	 1.00; 46/200 2.39 (0.52–11.03); 3/6 1.62 (0.76–3.44); 15/46 1.14 (0.49–2.66); 12/47 2.70 (1.02–7.17); 10/17	confounding
Brüning *et al.* 2003 (no overlap with Vamvakas *et al.* 1998)	Germany regional (Arnsberg) hospital-based 134 cases (83 M, 51 F) 401 hospital controls (225 M, 176 F) Self-assessed exposure including self-reported narcotic symptoms, JEM based on CAREX database (job titles) or British JEM for grouped solvents	*CAREX Database* Longest held job with TCE/Perc exposure (compared with no TCE) Any metal greasing/degreasing *Self-assessed TCE exposure* Ever Exposure + Narcotic symptoms Any Non-daily occurrence Daily occurrence Duration exposure (yr) No exposure < 10 10–19 20+ Time since 1st exp (yr) No exposure 5–9 10–19 20+ No increasing risks with time since last exposure	*OR* 1.80 (1.01–3.20); 117/316 5.57 (2.33–13.32); 15/11 2.47 (1.36–4.49); 25/38 3.71 (1.80–7.54); 19/18 4.60 (1.87–11.30); 13/10 5.91 (1.46–23.99); 5/4 1.00; 109/363 3.78 (1.54–9.28); 11/14 1.80 (0.67–4.79); 7/13 2.69 (0.84–8.66); 6/7 1.00; 109/363 3.21 (0.28–37.38); 1/2 1.50 (0.28–8.10); 2/6 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. Covariates: Sex, age, smoking; cases and controls had similar BMI Strengths: Appears reasonable that workers with self-reported exposure had high levels of exposure and exposure to other chlorinated solvents was unlikely. Limitations: Qualitative exposure assessment; possible selection bias *Evidence for a positive association:* Statistically significant, high effect estimates; unlikely to be explained by confounding

Reference	Study Size (N) Exposure assessment	Exposure groups	RR or OR (95% CI) # exposed cases/controls	Interpretation
Vamvakas *et al.* 1998	Germany regional hospital-based 58 RCC cases 84 hospital controls Expert assessment based on severity of pre-narcotic symptom and exposure duration using occupational history data from interviews	Ever TCE exposure *TCE exposure categories* No TCE exposure Low TCE exposure Medium TCE exposure High TCE exposure	*OR* 10.80 (3.36–34.75); 19/7 1.00; 39/77 6.61 (0.50–87.76); 2/2 11.92 (2.55–55.60); 9/3 11.42 (1.96–66.79); 8/2	High level of exposure (see Brüning *et al.*) Mean duration of exposure: 16 years cases, 7 years controls. Covariates: Age, sex, smoking, BMI, blood pressure, and diuretic intake Strengths: High level of confidence that workers had high level of exposure and exposure to other chlorinated solvents was unlikely Limitations: Potential selection bias (differential) away from the null *Evidence for a positive association:* Statistically significant, high effect estimates; unlikely to be explained by confounding or co-exposures; potential for biases would lead to an over-estimate of the risk estimate
Other occupational studies				
Christensen *et al.* 2013	Montreal, Québec (Canada) Population- and hospital-based 1975–1985 177 male RCC cases RCC 533 population-based controls 1999 cancer controls Expert assessment of	Ever exposure Substantial exposure	*OR (95%CI) #cases/#cancer controls/#population controls* 0.9 (0.4–2.4); 5/63/15 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 Covariates: age, census tract, median income, ethnicity, self vs. proxy respondent, smoking, alcohol consumption, coffee use, education Strengths: Adequate quality of exposure assessment Limitations: Low exposure

Reference	Study Size (N) Exposure assessment	Exposure groups	RR or OR (95% CI) # exposed cases/controls	Interpretation
	occupational data from interviews			prevalence resulting in low statistical power *Null:* No evidence for a positive association but limited utility
Pesch *et al.* 2000a	Germany Cancer registry study 935 (570 M, 365 F) RCC cases 4,298 (2,650 M, 1,648 F) registry control JEM and JTEM	*JTEM* Men No exposure Medium TCE exposure High TCE exposure Substantial TCE exposure Women No exposure Medium TCE exposure High TCE exposure Substantial TCE exposure	(Controls not reported) *OR* 1.00 1.3 (1.0–1.8); 68 1.1 (0.8–1.5); 59 1.3 (0.8–2.1); 22 *OR* 1.00 1.3 (0.7–2.6); 11 0.8 (0.4–1.9); 7 1.8 (0.6–5.0); 5	Prevalence of substantial TCE exposure was low among cases and varied by type of JEM. Covariates: Age, center, and smoking. Cases and controls did not differ in BMI, education, age, region, and smoking status and analgesics use. Strengths: Adequate number of exposed cases and controls Limitations: Potential for exposure misclassification *Limited evidence for a positive association*: Non-statistically significant elevated effect estimates
Dosemeci *et al.* 1999	Minnesota (USA) Registry-based 1988–1999 438 living cases RCC (273 M, 165 F); 687 population controls Qualitative JEM based on occupational data from interviews	Men Women Total	1.04 (0.6–1.7); 33 (controls NR) 1.96 (1.0–4.0); 22 (controls NR) 1.30 (0.9–1.9); 55 (controls NR)	Exposure prevalence to TCE among controls was 13%. Covariates: Age, sex, smoking, BMI, hypertension, use of diuretics or hypertension drugs Strengths: Adequate number of exposed cases Limitations: Exposure assessment only considered current and usual jobs, no assessment of intensity or duration of exposure.

Reference	Study Size (N) Exposure assessment	Exposure groups	RR or OR (95% CI) # exposed cases/controls	Interpretation
				*Limited evidence for a positive associatio*n: Moderate (borderline statistical significance) elevated effect estimate among women only

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 (NAS 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) because many studies have been published since the older evaluations. 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.* (2012) 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 Low sensitivity to removal of individual studies or selection of alternative RRs 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 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 Little evidence of heterogeneity and publication bias; Higher mRR among incidence vs. mortality studies
Karami *et al.* 2012a	TCE-exposed cohorts (9) *Exp.-Response* Long duration vs. Short duration (3) Subset of U-TCA studies (3)	1.26 (1.02–1.56)[a] 1.03 (0.59–1.78)	 1.52 (1.08–2.13) 0.90 (0.56–1.45)	Little evidence of heterogeneity or publication bias
Karami *et al.* 2012a	TCE-exposed case-control studies (9) *Exp.-Response* High intensity vs. Low intensity (6)	1.35 (1.17–1.57)[a]	 1.68 (1.23–2.30) 1.49 (1.02–2.17)[a]	Little evidence of heterogeneity or publication bias
Kelsh *et al.* 2010	TCE-exposed cohorts (8)	1.34 (1.07–1.67)[a]		Little evidence of heterogeneity or

Reference	Study design (# studies)	mRR (95% CI) All	mRR (95% CI) Highest exposure	Comments
	Exp.-Response Long duration vs. Short duration[b] (7) High cum. exp. vs. Low cum. exp.[b] (3)		1.24 (0.69–2.23) 1.50 (0.89–2.26) 1.39 (0.75–2.59) 1.29 (0.68–2.47)[a]	publication bias
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.* (2012), 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 for (or considered) 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).

Potential confounding from smoking can reasonably be ruled out. Smoking is a relatively weak risk factor for kidney cancer (~1.4 for current smoking in meta-analyses data), and the NAS (2006) estimated that it most likely would only account for ~10% increase in risk if smoking differences were 20% higher among trichloroethylene-exposed populations. Increased risks of kidney cancer were observed in several case-control studies that adjusted for or considered smoking habits (Brüning *et al.* 2003, Vamvakas *et al.* 1998, Charbotel *et al.* 2006, 2009, Moore *et al.* 2010, Pesch *et al.* 2000a, Dosemeci *et al.* 1999). 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 ranking of the utility of the studies to inform the cancer hazard evaluation or by 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.

Utility of the studies to inform the cancer hazard evaluation: Studies were ranked into categories of utility: 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 utility 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 these elements.)

Ranked estimated exposure: For each study the effect estimate and 95% CI for the highest exposure level was 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.* 2013). 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 effect 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 kidney 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 utility) studies (Charbotel *et al.* 2006, 2009, Moore *et al.* 2010, Zhao *et al.* 2005), and two studies with moderate or moderate to low utility, 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 utility (Hansen *et al.* 2013, Morgan *et al.* 1998), and some studies considered to have low to moderate utility (Dosemeci *et al.* 1999, Pesch *et al.* 2000a,) or low utility (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 utility 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 the 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 studies. The most recent meta-analyses (Scott and Jinot 2011, Karami *et al.* 2012) 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.* (2012). 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 lower 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.

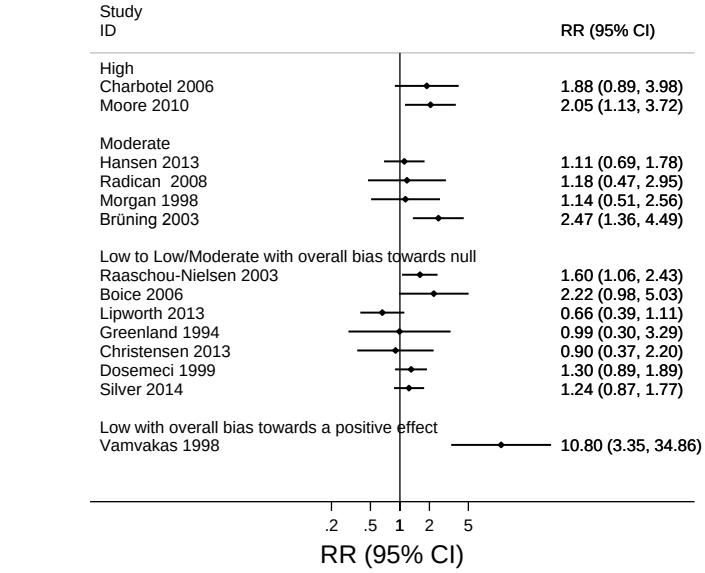
There was evidence for positive exposure-response relationships or higher risks in more highly or longer exposed groups in both cohort and case-control studies with several exposure metrics. Risks increased with increasing exposure intensity or cumulative exposure in the cohort study of aerospace workers (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.* (2012) 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 database was inadequate to evaluate the effect of latency, as few cohort or case-control studies conducted lagged vs. unlagged or time since first exposure analyses and data are generally sparse due to limited numbers of cases. SIRs for kidney cancer increased with increasing lagging time in the study of blue-collar workers (Raaschou-Nielsen *et al.* (2003) and were slightly higher (10%) in the 20-year lagged analysis compared with the 10-year lagged and unlagged analyses in the study of biomonitored workers (Hansen *et al*. 2013). However, no differences in effect estimates after lagging by varying periods of between approximately 0 and ≥ 20 years were reported in other studies (Vlaanderen *et al*. 2013, Moore *et al*. 2010, Zhao *et al*. 2005, Brüning *et al.* 2003). The rest of the studies did not conduct lagged analysis (Christensen *et al.* 2013, Lipworth *et al.* 2011, Radican *et al.* 2008, Boice *et al*. 2006, Charbotel 2006, 2009, Morgan *et al.* 1998, Henscher *et al*. 1995, Pesch *et al*. 2001, Dosemeci *et al.* 1999) or only reported effect estimates for one lagging period (Greenland *et al*. 1994, Bove *et al*. 2014) and Silver *et al.* 2014).

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

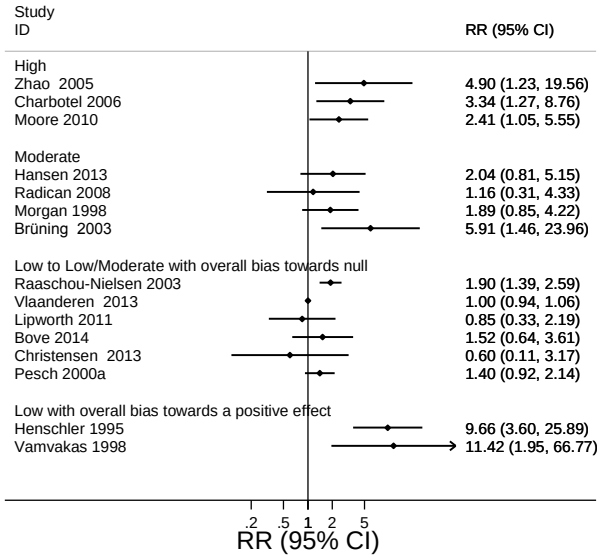
with renal cancer. Potential selection bias and confounding from smoking in the study of blue-collar workers does not explain all of the excess risk of kidney cancer associated with trichloroethylene exposure. Although information on occupational co-exposures is missing in most of the studies, the identified 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



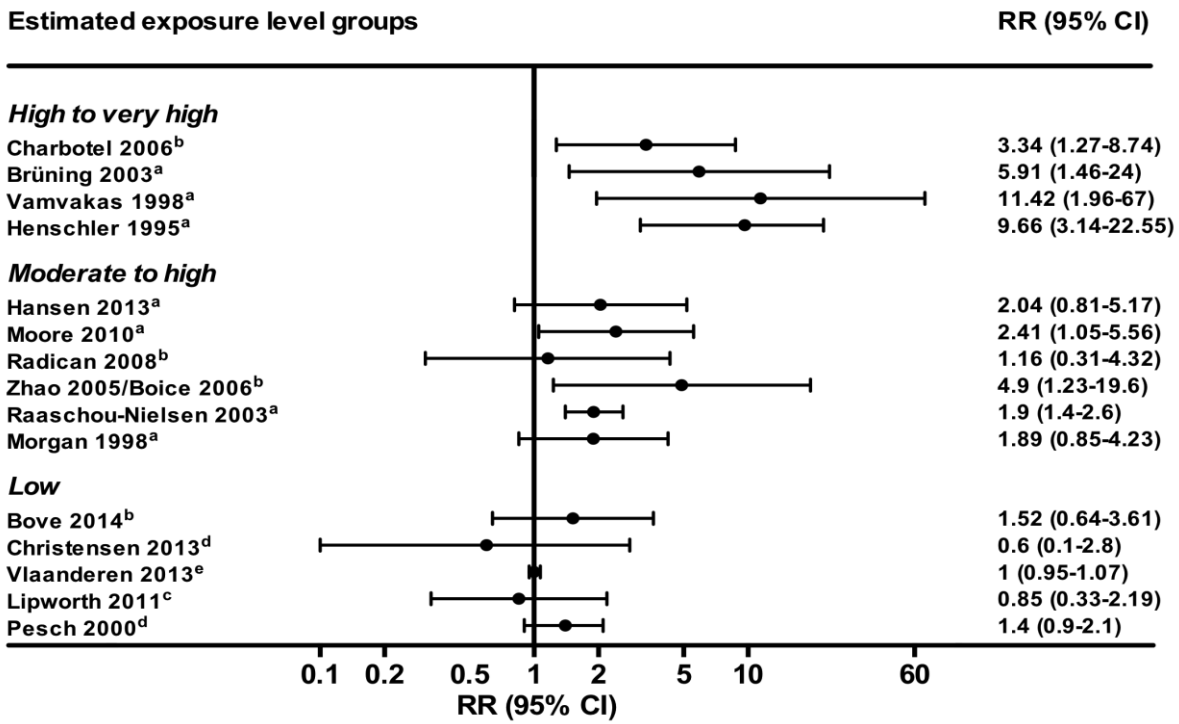
Relative risk and 95% CI for ever exposure to TCE and kidney cancer by study quality according to Section 4.1.3. Studies by Bove *et a*l. (2014) and Vlaanderen *et al*. (2013) are not graphed because they did not report relative risk for ever exposure but they are reported in Figure 4-3.

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 4.1 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 trichloroethylene-induced kidney carcinogenicity include key events attributed to GSH-conjugation-derived metabolites (genotoxicity and cytotoxicity) and those attributed to oxidative metabolites (peroxisome proliferation activated receptor α (PPARα) activation, α_{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. Modes of action associated with GSH-derived metabolites are discussed in Section 4.2.2 while those associated with oxidative metabolites are discussed in Section 4.2.3.

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. 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. 2. Cytotoxicity and compensatory cell proliferation. 3. Clonal expansion of initiated cells.
PPARα activation	1. Oxidative metabolites produced in the liver activate PPARα in the kidney. 2. Alterations in cell proliferation and apoptosis. 3. Clonal expansion of initiated cells.
α_{2u}-Globulin-related nephropathy (relevant only in male rats)	1. Oxidative metabolites cause hyaline droplet accumulation and an increase in α_{2u}-globulin resulting in nephrotoxicity. 2. Subsequent cytotoxicity, necrosis, and sustained regenerative tubule-cell proliferation. 3. Development of intraluminal granular casts from sloughed cellular debris associated with tubule dilation and papillary mineralization. 4. Foci of tubule hyperplasia in the convoluted proximal tubules. 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. 2. Increased formic acid causes cytotoxicity in the kidney. 3. Compensatory cell proliferation. 4. Clonal expansion of initiated cells.

Source: Adapted from EPA 2011a.

4.2.2 The proposed role of GSH-conjugation metabolites in kidney carcinogenicity

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.

The proposed key events for kidney carcinogenicity include (1) GSH-conjugation-derived metabolites produced *in situ* or delivered systemically to the kidneys, and (2) mutagenic, genotoxic (see Section 4.2.2.1) and cytotoxic effects (see Section 4.2.2.2) induced by these metabolites in the kidneys advance the acquisition of multiple critical traits contributing to carcinogenesis (EPA 2011a).

Disposition and toxicokinetic data (reviewed in Section 1) show that metabolites from the GSH-conjugation pathway are formed in the liver and kidneys and that flux through the GSH-pathway is more substantial than previous estimates based on urinary metabolites indicated. 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. 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 a large number of exposed kidney cancer cases (1,097) and controls (1,476), 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 among subjects with two deleted alleles (null genotype) (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. Thus, the findings of Moore *et al.* (2010) are consistent with the hypothesis that genes involved in the GSH-conjugation pathway are involved in trichloroethylene-induced renal cancer.

The other two studies had limited methods for evaluating potential effect modification. Brüning *et al.* (1997a) reported that having a GSTT1 or GSTM1 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 the Arnsberg area of Germany). 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.

4.2.2.1 Genotoxicity

Genotoxicity is a well-established cause of carcinogenicity. Although trichloroethylene was not mutagenic without metabolic activation in most standard bacterial assays, GSH-conjugation pathway-derived metabolites are genotoxic (see Section 2). Although there are some data limitations, the available evidence indicates that DCVC is a more potent mutagen than any of the oxidative metabolites (Moore and Harrington-Brock 2000). Positive genotoxicity data for GSH–derived metabolites were reported (primarily from *in vitro* assays). DCVG, DCVC, and NAcDCVC were mutagenic in the Ames test, and kidney-specific genotoxic effects also were reported (IARC 2014, EPA 2011a). DCVC and DCVG were direct-acting mutagens in some strains of *S. typhimurium*. Furthermore, the use of β-lyase inhibitors or kidney subcellular fractions for metabolic activation supported the importance of *in situ* metabolism in the genotoxicity of these metabolites in the kidney. 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).

Doses used in the *in vitro* assays were generally in the sub-nmol to nmol range for the Ames assay and in the μM to mM range with mammalian cells. Thus, many of the *in vitro* assays used concentrations higher than those observed *in vivo*. Lash *et al.* (1999b) reported maximum DCVG levels of approximately 110 nmol/mL (0.11 μM) in the blood of human volunteers exposed to trichloroethylene vapors (100 ppm) for 4 hours. DCVG concentrations were not measured in tissues but would likely have been higher in the kidney due to *in situ* metabolism and a trichloroethylene tissue:blood partition coefficient > 1 (see Section 1.1.1). The available *in vivo* data do show some genotoxic effects in target tissues (likely resulting from GSH-conjugated metabolites and including micronuclei and DNA single-strand breaks in the kidney) in rodents exposed to trichloroethylene. Other studies in rodents show that sufficient DCVC is formed *in vivo* from trichloroethylene metabolism to account for histological changes in the renal tubules (EPA 2011a).

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 Country	Study Type Population	Exposure Estimate Method	Findings Incidences	Comments
Brüning *et al.* 1997a Germany	Case-control 23 exposed	Semi-quantitative Work history and acute exposure symptoms	**Unable to assess mutation differences** 23/23 mutated in exposed 30% in exon 1 44% in exon 2 26% in exon 3	No unexposed controls or increase in mutations with higher exposure
Brauch *et al.* 1999 Germany	Case-control 44 exposed 107 controls	Low/medium/high Occupational hygienist	**Increased mutations** 33/44 mutated in exposed 54% in exon 1 39% at nucleotide 454 32% of mutations were multiple mutations 42/73 mutated in control 0% of mutations were multiple mutations	Number of mutations increased with higher levels of estimated exposure
Brauch *et al.* 2004 Germany	Case-control 17 (exposed) 21 (unexposed)	Low/medium/high Occupational hygienist	**Increased mutations** 14/17 mutated in exposed 39% at nucleotide 454 50% of mutations were multiple mutations 2/21 mutated in control	RCC cases exposed or unexposed to trichloroethylene Exposure decreased the age of diagnosis
Charbotel *et al.* 2007 France	Case-control 69 cases of RCC	Low/medium/high Expert-evaluated questionnaire	**No mutation differences** 2/23 mutated in exposed 2/25 mutated in control	Low rate of mutation and no difference in mutations with exposure Potential for exposure misclassification
Moore *et al.* 2011 Europe	Case series 470 sporadic clear cell RCC cases	Levels of exposure not reported Expert interview	**No mutation differences** 415/470 mutated in clear cell renal carcinoma 37% in exon 1 30% in exon 2 26% in exon 3	Level of exposure not reported. Only 1 unexposed case had mutation at nucleotide 454. 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) high incidences of proximal tubule cytomegaly and toxic nephropathy only in dosed male and female rats from five strains in chronic bioassays, (3) high incidences of proximal tubule cytomegaly only in dosed male and female mice in a chronic bioassay, (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 α, glutathione-S-transferase π, β_2-microglobulin, α_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 α_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. In addition, NTP (1988) reported high incidences of toxic nephropathy (17% to 80%) only in dosed rats from four strains that was not related to the common spontaneous nephropathy of aging rats. 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 Arem *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, DNA adducts in combination with toxic doses of trichloroethylene could lead to sustained regenerative cellular proliferation that promotes the selection, survival, and clonal expansion of mutated cells in the tubular epithelium.

4.2.3 Proposed modes of action associated with oxidative metabolites

As mentioned above, several modes of action associated with oxidative metabolites have been proposed (PPARα activation, α_{2u}-globulin-related nephropathy, and formic acid-related

nephrotoxicity). These modes of action have little to no experimental support and are briefly reviewed below.

4.2.3.1 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).

4.2.3.2 α_{2u}-Globulin-related nephropathy

α_{2u}-Globulin-related nephropathy is characterized by the rapid accumulation of protein droplets containing α_{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 α_{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 α_{2u}-globulin concentrations or cell replication in male or female rats exposed to trichloroethylene but some effects were consistent with α_{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 α_{2u}-globulin nephropathy is a factor in trichloroethylene-induced kidney carcinogenesis in rats.

4.2.3.3 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.

4.2.4 Summary

The mode of action for trichloroethylene-induced kidney cancer is not completely understood but the available data provide support for a mutagenic and cytotoxic mode of action mediated by GSH-conjugated metabolites. There is experimental evidence that GSH metabolites (particularly DCVC) 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 several of 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 constituting about 4.3% of all new cancer cases per year in the United States. The U.S. age-adjusted incidence rate for NHL is approximately 24 and 16 cases per 100,000 per year in men and women, respectively (2007 to 2011 rates; SEER 2014b) compared with approximately 8 and 5 per 100,000 deaths per year in men and women, respectively, due to a 70% 5-year survival rate, an increase from approximately 46% in 1975. NHL rates in other European countries (see e.g., Clarke and Glaser 2002, Muller *et al.* 2005, Adamson *et al.* 2007, Ferlay *et al.* 2013, 2014), from which the studies included in the evaluation are drawn, appear to be broadly similar, but with some variations. For example, U.K age-standardized incidence rates (2011) are approximately 18 and 13 per 100,000 per year in men and women, respectively, with a similar 5-year survival rate of approximately 63% (Cancer Research UK 2014b) although diagnosed incidence was approximately half that of the U.S. in 1975. Studies reporting incidence are generally more informative than mortality studies. The latencies of lymphohematopoietic cancers such as NHL are generally less than for solid tumors, but vary widely; they may be as low as 1 or 2 years in association with some exposures (Howard 2013). Incidence rates generally increase steeply after approximately 50 years of age.

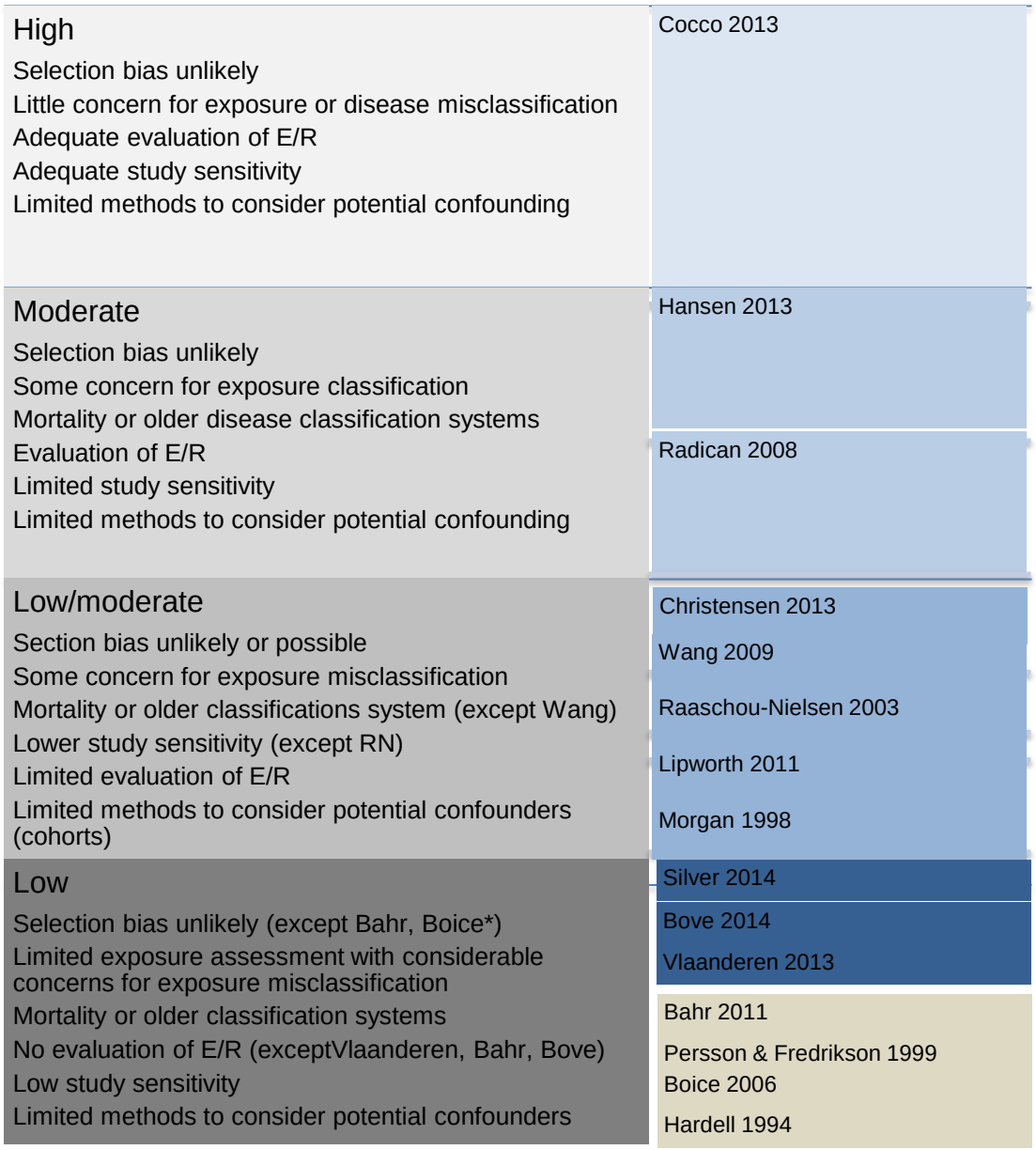
Multiple myeloma is a rare cancer, comprising approximately 0.8% of all cancers. U.S. incidence and mortality rates for multiple myeloma are approximately 6 per 100,000 and 3.4 per 100,000 per year (2007 to 2011), respectively (SEER 2014c), again suggesting that the studies reporting incidence rates 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. (No comparable data for these specific subtypes was identified for the United Kingdom and other European countries were identified.)

The incidence rate for NHL in Europe and the Nordic countries has roughly quadrupled from the 1950s to the late 1990s and doubled from the 1970s to the 1990s (Adamson *et al.* 2007) but has then stabilized in the past decade or more. A broadly similar pattern has been observed in the United States (Clarke and Glaser 2002, with increases in incidence in the United States now slowing to approximately 0.5% per year over the past decade (see U.S. SEER rates). However, no study has yet adequately examined to what extent observed changes in temporal trends are

attributable to changes in classification systems, or diagnostic improvements or changes in registration methods rather than true changes in incidence (Adamson *et al*. 2007), particularly as variations in these trends are observed among different age and racial subgroups (e.g., Clarke and Glaser 2002). As noted in Section 3, classification and coding systems for NHL and its subtypes have changed considerably over the past twenty years, so that comparisons of incidence rates across different studies conducted over different calendar periods should be interpreted with caution. In addition, earlier studies of NHL generally do not report subtypes, which do not reflect the histological and possibly biologically distinct heterogeneity of the disease (Clarke and Glaser 2002) and differences in rates and trends for subtypes, e.g., follicular lymphoma. In the available studies in the present evaluation, 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 elements related to the utility to inform the hazard evaluation (such as study sensitivity) 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 the overall utility of the study. 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 Study utilty ranking: NHL



Grey: Utility to inform hazard evaluation; light grey – highest. Blue: Overall potential biases towards the null or lower sensitivity; light blue –most sensitive or least biased. Tan: Multiple limitations; overall direction of potential biases unknown. Morgan (1998) was rated somewhat lower for NHL than kidney or liver cancer because of fewer expected and exposed cases. *Selection bias possible for external but not internal analysis.

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, hazard rations (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 one each in Montreal (Christensen *et al.* 2013) and Connecticut (Deng *et al.* 2013/Wang *et al.* 2009a), 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.* 2009a) 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.* 2011a) 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.* 2009a), 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.* 2011a), 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-hour 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-hour and 3.3, 95% CI = 1.1 to 10.01 for greater than 234,000 ppm-hour). Estimated (not measured) exposures for a proportion of the workers were high (> 234,000 ppm-hour 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.* 2009a) 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); however, this study's limitations include potential for exposure misclassification, including recall bias, use of proxy as controls, the minimum requirement to be classified as exposed was less than one week of continuous exposure in this study, potential confounding from exposure to other agents including other organic solvents, and small numbers of cases and controls. The other Swedish study by Persson and 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-hour. This study used the same detailed exposure assessment as Purdue *et al.* (2011a). 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.* 2011a). In the case-control study among Connecticut women (Deng *et al.* 2013/Wang 2009a), 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 Population # Exposure assessment	Exposure groups	External or additional analyses SMR, SIR (95% CI) # cases/deaths	Internal analysis RR, SRR, HR or OR (95% CI) # exposed cases/deaths or cases/controls	Interpretation
Nordic studies					
Vlaanderen *et al.* 2013	Population-based of 5 Nordic countries, linkage of cancer registry with census questionnaire M: 44,708 cases, 223,540 controls F: 31,422 cases, 157,110 controls Semi-quantitative JEM	*Cumulative exp. (median unit-yr)* 0 0.04 0.13 0.72 *High exposure group (median*) Cumulative (0.83 unit-yr) Intensity × prevalence (0.04 unit)		*ICD-7: 200, 202* *HR incidence* 1.00 1.01 (0.95–1.07); 1,213 0.93 (0.88–1.00); 1,183 0.97 (0.91–1.03); 1,211 0.95 (0.84–1.06); 353 0.96 (0.84–1.09); 269	Low prevalence of exposure (TCE) and exposure levels likely to be low Covariates: Age, sex, country Strengths: Long follow-up, large numbers of cases Limitations: Misclassification of exposure likely; JEM had poor sensitivity and did not account for heterogeneity within jobs and over time; TCE exposure correlated with tetrachloroethylene exposure *Null:* No evidence for a positive association but limited utility due to low TCE levels and exposure misclassification
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 5553 (3776 M, 1777 F) Biomonitoring (U-TCA)	*Hansen* et al. *2013* Men Women Men & women <u>Lag analysis (yr)</u> 0 10 20 <u>U-TCA (mg/L)</u> < 5	*ICD-7: 200, 202* *SIR* 1.55 (1.06–2.20); 32 0.63 (0.23–1.37); 6 1.26 (0.89–1.73); 38 1.21 (0.83–1.71); 32 1.11 (0.68–1.72); 20	*ICD-7:200,202* *HRR incidence (no lag)* 1.0; 12	Low exposure levels (only 20% exposed to ≥ 20 ppm) and short duration of employment Covariates: Age, sex, calendar period; indirect consideration of smoking and alcohol consumption Strengths: Biomonitoring data,; large numbers of workers ever exposed. Limitations: Only 2 or 3 U-

Reference	Study name Population # Exposure assessment	Exposure groups	External or additional analyses SMR, SIR (95% CI) # cases/deaths	Internal analysis RR, SRR, HR or OR (95% CI) # exposed cases/deaths or cases/controls	Interpretation
		5–25 25–50 > 50 P_{trend}		1.16 (0.53–3.09); 14 1.56 (0.63–3.81); 8 0.66 (0.21–2.03); 4 0.79	TCA measurements per individual and unlikely to estimate lifetime or cumulative exposure; low statistical power for evaluating modest risks; limited ability to evaluate exposure-response relationship *Limited evidence for a positive association:* Statistically significant, moderately elevated effect estimate among men only; decreased risk with increasing exposure
Raaschou-Nielsen *et al.* 2003 (Potential overlap with Hansen *et al.* 2013)	Danish blue collar workers 40,049 M+F (approx. 70% M) Working at a company using TCE	*Higher TCE exposure subcohort* *Ever exposed* Lag time (yrs) 0–9 10–19 ≥ 20 Duration employment (yrs) 1–4 ≥ 5 Yr. of 1st employment Before 1970 1970–1979	*ICD-7: 200, 202* *SIR* 1.5 (1.0–2.0) 65 1.8 (0.9–3.1); 12 1.3 (0.8–2.0); 22 1.7 (1.1–2.4); 31 1.5 (1.1–2.1); 35 1.6 (1.1–2.2); 30 1.6 (1.1–2.3); 35 1.5 (1.0–2.1); 30	NR	Higher levels of TCE prior to 1970 (40–60 ppm); low levels of exposure after that time Covariates: Age, sex, calendar year Strengths: Large numbers of exposed cases; subcohort of subjects with higher exposure potential. Limitations: Young cohort; possible selection bias for difference in SES; external analysis only; possible exposure misclassification *Evidence for an association*: Statistically significant, moderate elevated effect estimates but little evidence of

Reference	Study name Population # Exposure assessment	Exposure groups	External or additional analyses SMR, SIR (95% CI) # cases/deaths	Internal analysis RR, SRR, HR or OR (95% CI) # exposed cases/deaths or cases/controls	Interpretation
					an exposure response
Aerospace and aircraft workers					
Lipworth *et al.* 2011 (update Boice *et al.* 1999)	Burbank, CA (USA) aircraft manufacturing workers N = 5,443 (approx. 80% M) Individual work histories (JEM)	TCE cohort (ever exposed) *TCE: years exposed* 0 < 1 1–4 5+ P_{trend}	*ICD (time of death) SMR* 1.31 (0.97–1.73); 50	*ICD (time of death) RR mortality* 1.00; 50 0.84 (0.48–1.47); 18 1.10 (0.59–2.04); 14 1.02 (0.55–1.90); 15 > 0.20	Exposure levels not reported; short exposure duration Covariates: Age, date of birth, date of hire, termination date, sex and race Strengths: Long follow-up, adequate number of cases and controls for ever exposure 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. *Limited evidence for a positive association*: Elevated effect estimate (approaching statistical significance) for ever exposure; no evidence of an exposure response relationship
Radican *et al.* 2008 (mortality to 2000) Blair *et al.* 1998 (incidence	Utah (USA) aircraft maintenance workers N = 7,204 (5,153 M, 1,051 F)	*Ever-exposed (M & F)* 1990 follow-up: mortality 2000 follow-up: mortality Mortality; 2000 follow-up	*ICDA-8, ICD-9, 10 200, 202, or C82-8* *Internal analysis HR mortality*	*ICDA-8, ICD-9,10: 200, 202, or C82-85 HR mortality* 2.0 (0.9–4.5); 28 1.36 (0.77–2.39); 46 *Internal analysis HR mortality*	Estimated exposure: Most workers exposed to low levels (~10 ppm), modest number of workers exposed to higher levels (~100 ppm) Covariates: Age, calendar year

Reference	Study name Population # Exposure assessment	Exposure groups	External or additional analyses SMR, SIR (95% CI) # cases/deaths	Internal analysis RR, SRR, HR or OR (95% CI) # exposed cases/deaths or cases/controls	Interpretation
1973–1990) Note: mortality only updated by Radican)	Individual work histories (JEM)	Cumulative exp. (unit-yr)[a] All 0–5 2–25 > 25 Exposure category Low intermittent Low continuous Peak infrequent Peak frequent *Incidence (1990) follow-up* Cumulative exp (unit-yr) None 0–5 2–25 > 25	Women 1.18 (0.49–2.85); 9 1.48 (0.47–4.66); 4 0 1.30 (0.45–3.77); 5 1.39 (0.48–4.03); 5 1.03 (0.23–4.68); 2 3.45 (0.96–12.37); 3 1.27 (0.47–3.45); 6 Less than 3 exposed cases	Men 1.56 (0.72–3.35); 37 1.83 (0.79–4.21); 18 1.17 (0.42–3.24); 7 1.50 (0.61–3.69); 12 1.50 (0.67–3.34); 25 1.74 (0.76–3.97); 20 1.90 (0.69–5.24); 7 1.57 (0.67–3.69); 16 *RR incidence* 0.5 (0.2–1.7); 5 0.9 (0.3–2.6); 8 0.7 (0.2–2.6); 4 1.0 (0.4–2.9); 7	and sex Strengths: Adequate semi-quantitative JEM, long follow-up, adequate statistical power for ever exposure Limitations: Potential for exposure misclassification because of missing information for some workers; limited power due to low numbers of higher exposed workers; long follow-up time (45 years) may be past induction time; cannot rule out confounding from other co-exposures *Limited evidence for a positive association:* Statistically non-significant elevated effect estimates for ever exposure and some subgroup analyses
Boice *et al.* 2006 (Overlaps with Zhao *et al.* 2005)	Los Angeles (USA) Rocket engine testing workers 1,111 Men Qualitative JEM; Individual work histories	Ever exposed to TCE	*ICD-9; 200-2010 SMR* *(0.01–1.18) 1*	0.21 0.01–1.18; 1	Exposure occurs during text engine flush, which is likely to be high. Covariates: Date of birth, year of hire, pay type (surrogate for SES) and exposure to hydrazine Strengths: Adequate follow up Limitations: Qualitative exposure assessment; one exposed death

Reference	Study name Population # Exposure assessment	Exposure groups	External or additional analyses SMR, SIR (95% CI) # cases/deaths	Internal analysis RR, SRR, HR or OR (95% CI) # exposed cases/deaths or cases/controls	Interpretation
					Null: Limited utility (only 1 exposed death)
Morgan *et al.* 1998	Arizona aircraft manufacturing workers N = 4,733 (2,555 M, 2,178 F) Semi-quantitative JEM; individual work history	All TCE exposed workers *Cumulative exp. score* Low (2,357) High (2,376) Peak (med/high) vs. low/no	*ICD 7-9: 200* *SMR* 0.96 (0.20–2.81); 3 1.79 (0.22–6.46); 2 0.50 (0.01–2.79); 1	*ICD 7-9: 200* *RR mortality* 1.36 (0.35–5.21) 3 2.25 (0.46–11.09); 2 0.81 (0.10–6.49); 1 1.31 (0.28–6.08); 2	High exposure jobs were considered to be ≥ 50 ppm Covariates: age at hire, gender (decade at high considered but no effect) Limitations: Evidence of a HWE; potential exposure misclassification among low/medium exposure groups; mortality analysis and few exposed cases; inadequate statistical power because of few cases and ICD for NHL does not include 202 *Limited evidence for a positive association*: Elevated, but imprecise, effect estimate based on few cases and no consistent patterns
Other occupational studies					
Silver *et al.* 2014	New York State (USA) micro-electronics manufacturing workers 3,113 TCE exposed	5 modified exposure years (exposure duration modified by exposure potential)	NR	*ICD time of death* *HR* 0.87 (0.57–1.35) NR	Exposure levels NR. Only 13.9% of cohort exposed. 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

Reference	Study name Population # Exposure assessment	Exposure groups	External or additional analyses SMR, SIR (95% CI) # cases/deaths	Internal analysis RR, SRR, HR or OR (95% CI) # exposed cases/deaths or cases/controls	Interpretation
	Semi-quantitative JEM				employment duration prior to 1966 Limitations: Evidence of HWE. Exposure classification based on potential exposure and duration and only one cumulative exposure variable reported in analysis. Young cohort with only 17% deaths *Null*: No evidence for a positive association but limited utility based on limited exposure assessment and limited study sensitivity
Bahr *et al.* 2011	Kentucky (USA) Uranium enrichment workers 5,535 (M) Generic JEM	TCE exposure probability category 0 0–1 2–3 0–3 4–5 Total TCE exposure category 1 2 3 Total	ICD NR SMR 3.20 (0.39–11.57); 2 1.85 (0.85–3.52); 9 1.70 (0.88–2.97); 12 1.76 (1.09–2.69); 21 1.05 (0.52–1.88); 11 1.49 (1.02–2.10); 32	ICD NR *SRR mortality* 1.0 1.31 (0.47–3.65) 0.75 (0.27–2.12) 0.99 (0.40–2.46)	No information on exposure levels. Covariates: Age, sex, race (unclear) Limitations: Unclear descriptions of methods and findings; limited statistical power; evidence of HWE hire and survival bias. *Null:* No evidence for an association (internal analysis) but limited utility
Environmental exposure					
Bove *et al.* 2014	North Carolina (USA) (Camp Lejeune)	*Cumulative TCE (µg//L-months)* ≤ 1		*ICD NR* *HR mortality; 10-yr lag* 1.0 (27)	Estimated mean levels (µg/L-month) TCE from water supply = 358.7; overall cumulative

Reference	Study name Population # Exposure assessment	Exposure groups	External or additional analyses SMR, SIR (95% CI) # cases/deaths	Internal analysis RR, SRR, HR or OR (95% CI) # exposed cases/deaths or cases/controls	Interpretation
	154,932 Drinking water contamination - Ecological assessment	> 1–3100 > 3100–7700 > 7700–39745		0.90 (0.42–1.92); 10 0.75 (0.33–1.70); 8 1.15 (0.56–2.34); 13	exposure = 6,369 (median) and 5,289 (mean); 20% were exposed to levels between 7,700 and 39,745 Covariates: Sex, race, rank, 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 Strengths: Large cohort; adequate modeling of exposures Limitations: Young cohort; no information on individual water consumption; potential confounding from other contaminants e.g., tetrachloroethylene *Null:* Small increase in effect estimate but limited utility based on limited study sensitivity and exposure assessment

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) Population- and hospital-based 1975–1985 NHL: 215 cases, 2,341 cancer controls Expert assessment of occupational data from interviews	Ever exposed Substantial exposure	*ICD-9 200, 202* 1.2 (0.5–2.9); 7/65[b] 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 Covariates: age, census tract, median income, ethnicity, education, self vs. proxy respondent, smoking, alcohol assumption, coffee use Strengths: Adequate quality of exposure assessment Limitations: Low statistical power *Null:* Small increase risk for ever-exposed but limited utility based on 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) Population-based NHL: 3,788 cases, 4,279 controls Questionnaires on occupational history, industrial hygiene reports, expert assessments	High probability exposure *P f*or Fisher combined probability All exposed *Duration (yr)* No exposure 1–14 15–29 30–39 40+ P_{trend} *Intensity (ppm*) ≤ 5 5–75	*NHL (all subtypes) InterLymph consortium classification*[c] 1.4 (0.9–2.1); 50/38 0.04 1.0; 3,453/3,903 0.7 (0.4–1.5); 15/23 1.9 (0.8–4.3); 17/9 2.8 (1.0–7.8); 15/5 3.3 (0.3–33); 3/1 0.009 1.1 (0.4–3.0); 8/8 1.3 (0.8–2.2); 33/25	Exposure prevalence: 9% ever exposed; 1% high probability of exposure. Exposure levels not measured but high exposure categories are > 75 ppm Covariates: age, sex, study location Strengths: Good exposure and disease assessment; analysis of NHL subtypes Limitations: Reduced statistical power in NHL subtype analysis, no adjustment for lifestyle factors or co-exposures *Evidence for a positive association:* Statistically significant association with NHL; Evidence for exposure-response relationship

Reference	Study Size (N) Exposure assessment	Exposure groups	RR or OR (95% CI) # exposed cases/controls	Interpretation
		> 75 P_{trend}	2.2 (0.7–6.7); 9/5 0.059	
Deng *et al.* 2013 Wang *et al.* 2009a	Connecticut (USA) All NHL: 601 cases, 717 controls Questionnaire on occupational history. Linkage of occupation code to JEM	*Wang* et al. *2009a* Ever exposed Exposure intensity Low intensity Medium/high intensity P_{trend} *Deng* et al. *2013 polymorphism* *Ever exposed* IL12A_07 genotype TT AA *P* interaction	*ICD-O-2; OR* 1.2 (0.9–1.8); 77/79 1.1 (0.8–1.6); 64/71 2.2 (0.9–5.4); 13/8 0.06 *NHL (ICD-O-2)* 0.70 (0.34–1.42); 14/26 2.09 (1.28–3.42); 51/31 0.009	No cases or controls with high probability of exposure and medium/high exposure. Exposure prevalence 8% Covariates: Age, history of hematopoietic cancer, race, and alcohol consumption. Smoking, medial history of immune diseases, income, education level did not affect OR Strengths: Consideration of potential confounding from lifestyle factors, analyses by genotype & NHL subtype Limitations: Limited JEM (not calendar year specific and based on occupations not job tasks), no control for co-exposures *Evidence for a positive association:* Statistically significant, moderate elevated effect estimate in genotype analysis; some evidence for an exposure-response relationship
Persson and Fredrikson 1999	Sweden Population-based NHL: 199 cases, 479 controls Questionnaire on occupational history	Ever exposure	*ICD-8 used in 2nd study, NR 1st study* 1.2 (0.5–2.4); 16/32	Exposure prevalence 1% in controls Covariates: Age, sex Limitations: Limited exposure assessment, potential for exposure misclassification is substantial. *Null:* Small increase in risk but limited utility due to concern about exposure misclassification
Hardell *et al.* 1994	Sweden Population-based NHL: 105 cases, 335 controls Questionnaire on occupational history and leisure activities	Ever exposed	*Rappaport classification* 7.2 (1.3–4.2); 4/4	Exposure prevalence: 1% in controls Covariates: Age, vital status Limitations: Limited exposure assessment, and potential for exposure misclassification is substantial

Reference	Study Size (N) Exposure assessment	Exposure groups	RR or OR (95% CI) # exposed cases/controls	Interpretation
				Limited evidence for an association: Statistically significant, high elevated effect estimate; methodological concerns and small numbers of exposed cases/controls may bias towards an overestimate of the risk estimate.
Purdue *et al.* 2011a[d] incorporated in pooled analysis (Cocco *et al.* 2013)	U.S. SEER registry Population-based NHL: 1,189 cases, 982 controls Interviews on occupational histories and exposures; expert assessment by industrial hygienists based on questionnaire data and systematic industrial hygiene literature review	Exposure-response analyses *Average exposure* Per 90 ppm-hr/wk[e] P_{trend} > 360 ppm-hr/wk *Average exp. intensity* Per estimated 99 ppm P_{trend} *Exposure duration (yr)* Per 10 yr P_{trend} *Cumulative exposure* Per 65,520 ppm-hr P_{trend} > 234,000 ppm-hr	*ICD-O-2* *OR (# cases NR)* 1.11 (1.02–1.21) 0.02 7.9 (1.8–34.3) 1.18 (0.80–1.76) 0.41 1.13 (0.85–1.51) 0.40 1.10 (0.99–1.22) 0.08 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 Covariates: Age, sex, race, education level, and study area 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 Limitations: Reduced statistical power in NHL subtype analysis, no adjustment for lifestyle factors or co-exposures *Evidence for a positive association:* Evidence for exposure response relationship with multiple exposure metrics.

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					
Vlaanderen *et al.* 2013	*Cumulative exp. (unit-yr*) 0 0.04 0.13 0.74 *High exposure group* Cumulative (0.83 unit-yr) Intensity × prevalence (0.04 unit)	NR	NR	NR	*ICD-7; HR (incidence)* 1.00 0.93 (0.84–1.03); 468 0.92 (0.84–1.01); 574 0.96 (0.88–1.06); 541 1.01 (0.84–1.22); 132 1.03 (0.88–1.22); 134
Hansen *et al.* 2013	 Men Women Men & women	NR	NR	NR	*ICD-7; SIR* 0.47 (0.13–1.20); 4 1.04 (0.29–2.67); 4 0.65 (0.28–1.27); 8
Raaschou-Nielsen *et al.* 2003	*Entire cohort* Men (588,047 pyar) Women (118,270 pyar)	NR	NR	NR	*ICD-7; SIR* 1.1 (0.70–1.52); 28 0.90 (0.18–2.56); 3
Lipworth *et al.* 2011	 Ever exposed *TCE: years exposed* 0 < 1 1–4 5+ P_{trend}	NR	NR	0.93 (0.40–1.83); 8	*ICD time of death: SMR* 1.21 (0.76–1.81); 23 *RR mortality* 1.00 0.70 (0.31–1.58); 8 1.45 (0.68–3.09); 10 0.67 (0.25–1.83); 5 > 0.20
Radican *et al.* 2008 Mortality	 *Ever exposed M & W* *Cumulative exp. (unit-yrs)* Men[a] All 0–5 2–25 > 25	NR	NR	NR	*HR mortality (ICDA-8, ICD-9 and 10)* 1.35 (0.62–2.93); 25 1.08 (0.43–2.71); 19 0.69 (0.21–2.27); 5 1.58 (0.53–4.71); 7 1.19 (0.40–3.54); 7

Reference	Exposure group	DLBCL	Follicular lymphoma	CLL	Multiple myeloma
Cohort and nested case-control studies					
Blair *et al.* 1998 Incidence (RR) Same population as Radican *et al.*	*Ever exposed M& W* *Cumulative exposure Men*[b] No exposure < 5 5–25 > 25	NR	NR	NR	ICD NR RR (incidence) 1.3 (0.5–3.4); 14 1.7 (0.5–5.5); 10 1.0 (0.2– 4.2); 4 0.8 (0.1–4.4); 2 1.2 (0.3–4.7); 4
Boice *et al.* 2006				*ICD-9; SMR* 0.21 (0.01–1.1.8) 1	*ICD-9; SMR* 0.50 (0.01–2.77) 1
Silver *et al.* 2014	5 modified exposure duration yr (exposure duration modified by exposure potential)				*ICD time of death (HR mortality)* 1.18 (0.70–1.99) NR
Yiin *et al.* 2009 Nested case-control study	Average cumulative TCE exposure score/100				*OR (ICD-8)* 1.02 (0.98-1.05) NR
Bove *et al.* 2014	Cumulative (µg//L-mth) ≤ 1 > 1–155 > 155–380 > 380–8,585	NR	NR	NR	HR (ICD NR) 1.0; 6 2.09 (0.66–6.62); 7 1.29 (0.34–4.88); 4 0 cases
Case-control studies (OR)					
Cocco *et al.* 2013 Pooled analysis	Intensity (ppm) ≤ 5 5–75 > 75 P_{trend}	*InterLymph classification*[a]*; OR* 1.2 (0.3–4.4); 3/8 0.6 (0.2–1.6); 5/25 2.0 (0.5–8.7); 3/5 0.114	*InterLymph classification*[a]*; OR* 1.1 (0.1–9.2); 1/8 1.7 (0.7–4.1); 7/25 1.5 (0.2–13); 1/5 0.10	*InterLymph classification*[a]*; OR* 1.4 (0.3–7.0); 2/8 1.7 (0.7–4.0); 7/25 3.2 (0.6–18); 2/5 0.055	NR
Purdue *et al.* 2011a Incorporated into the pooled analysis	*Average exposure* Per 90 ppm-hr/week P_{trend} *Cumulative exposure* Per 65,520 ppm-hrs P_{trend}	ICD-O-2; OR 1.11 (1.01–1.23) 0.03 1.07 (0.94–1.22) 0.29	ICD-O-2; OR 1.15 (1.04–1.28) 0.005 1.17 (1.04–1.32) 0.01	ICD-O-2; OR 1.09 (0.96–1.24) 0.16 1.11 (0.96–1.27) 0.16	NR

Reference	Exposure group	DLBCL	Follicular lymphoma	CLL	Multiple myeloma
Cohort and nested case-control studies					
Cocco *et al.* 2010 Incorporated into pooled analysis	 Ever exposed *Cumulative exposure* Low exposure Medium exposure High exposure P_{trend}	*2001 WHO REAL classification; OR* 0.7 (0.4–1.1); 17 0.7 (CI NR); 6/37 0.4 (CI NR); 4/43 0.9 (CI NR); 7/37 0.16	*2001 WHO REAL classification; OR* 1.2 (0.6–2.3); 11 2.4 (CI NR); 7/37 0.3 (CI NR); 1/43 1.0 (CI NR); 3/37 0.65	*2001 WHO REAL classification; OR* 0.9 (0.5–1.5); 18 1.0 (CI NR); 6/37 0.4 (CI NR); 3/43 1.2 (CI NR); 9/37 0.94	*2001 WHO REAL classification; OR* 0.6 (0.3–1) 0.2 (CI NR); 1/37 0.7 (CI NR); 4/43 0.8 (CI NR); 4/37 0.22
Deng *et al.* 2013/Wang *et al.* 2009a	*Ever exposed* IL12A_07 genotype TT AA *P* interaction	*2001 WHO REAL classification; OR* 0.59 (0.19–1.85); 4 2.66 (1.42–4.96); 21 0.0119	*2001 WHO REAL classification; OR* 0.82 (0.25–2.72); 4 1.71 (0.78–3.77); 10 0.3498	NR	NR
Gold *et al.* 2011 Seattle Region (SEER)	High confidence 10-yr lag *Cumulative exposure* No exposure 1–415 416–3,000 3,001–6,592 6,593–49,500 P_{trend}	NR	NR	NR	*ICD-O-2/3; OR* 1.0; 139/409 1.1 (0.4–2.9); 6/18 1.6 (0.7–3.5); 11/20 1.4 (0.5–3.8); 6/16 2.3 (1.1–5.0); 18/18 0.02
Costantini *et al.* 2008 Italy	Exposure intensity Very low/low Medium/high ≤ 15 years' exposure > 15 years' exposure P_{trend}			*ICD-9; OR* 1.2 (0.5–2.7); 8/47 0.9 (0.3–2.6); 4/35 0.7 (0.1–3.4); 2/24 1.2 (0.2–6.2); 2/11	*1CD-9; OR* 1.5 (0.7–3.5); 9/28 0.9 (0.3–2.4); 5/27 0.5 (0.1–2.3); 2/19 1.3 (0.3–5.9); 8/13 0.82
Nordstrom *et al.* 1998	 Ever exposed			*HCL (ICD NR); OR* 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 2011a, Scott and Jinot 2011, Karami *et al.* 2013). 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) because many studies have been published since the older evaluations. 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 2011a/Scott and Jinot 2011	Combined cohort and case-control studies Any exposure (17) High exposure (13)	1.23 (1.07–1.42)[b]	1.43 (1.13–1.82)	Random effects model Low sensitivity to removal of individual studies or selection of alternative RRs Low to moderate heterogeneity; some evidence of publication bias
EPA 2011a/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 2011a/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 Little evidence of heterogeneity and publication bias
Karami *et al.* 2013	TCE-exposed cohorts (10) *Exp-response*: Long duration Short duration High intensity [c] Low intensity Subset of U-TCA studies (3)	1.52 (1.29–1.79) 2.15 (1.34–3.45)	 1.56 (1.02–2.40) 1.30 (0.92–1.84) 1.27 (0.83–1.96) 1.68 (1.14–2.46)	Some evidence of positive exposure response among a total of 4 studies using measures of duration 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) *Exp-response*: Long duration Short duration High intensity Low intensity	1.14 (0.93–1.40)	 1.18 (0.60–2.34) 1.46 (0.78–2.73) 1.42 (0.86–2.33) 1.06 (0.79–1.42)	Some evidence of publication bias 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 2011a/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. They also calculated meta-relative risks among studies conducted across two different calendar time periods (divided by the median year of publication), and observed no differences for cohort studies of NHL and kidney cancer (but an increase in mRR for case-control studies of kidney cancer conducted since 1995). The latter finding, according to the authors, suggested "possible improvements" in the validity and reliability of exposure assessment methods in case-control studies (Karami *et al.* 2013).

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). Other organic solvents, and possibly other exposures, may be co-exposures in two of the Swedish studies (Nordstrom *et al.* (1998), Hardell *et al.* 1994). 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.* 2009a, 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.* 2011a) 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 and NHL based on findings of a modest increase in risk of NHL in several studies with 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 utility (Lipworth *et al.* 2011, Morgan *et al.* 1998, Raaschou-Nielsen *et al.* 2003, Deng *et al.* 2013/Wang *et al.* 2009a). 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 because it was based on small numbers of exposed cases and controls and this study had several methodological limitations. 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 utility, 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.* (2011a) 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.* 2009a) 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.

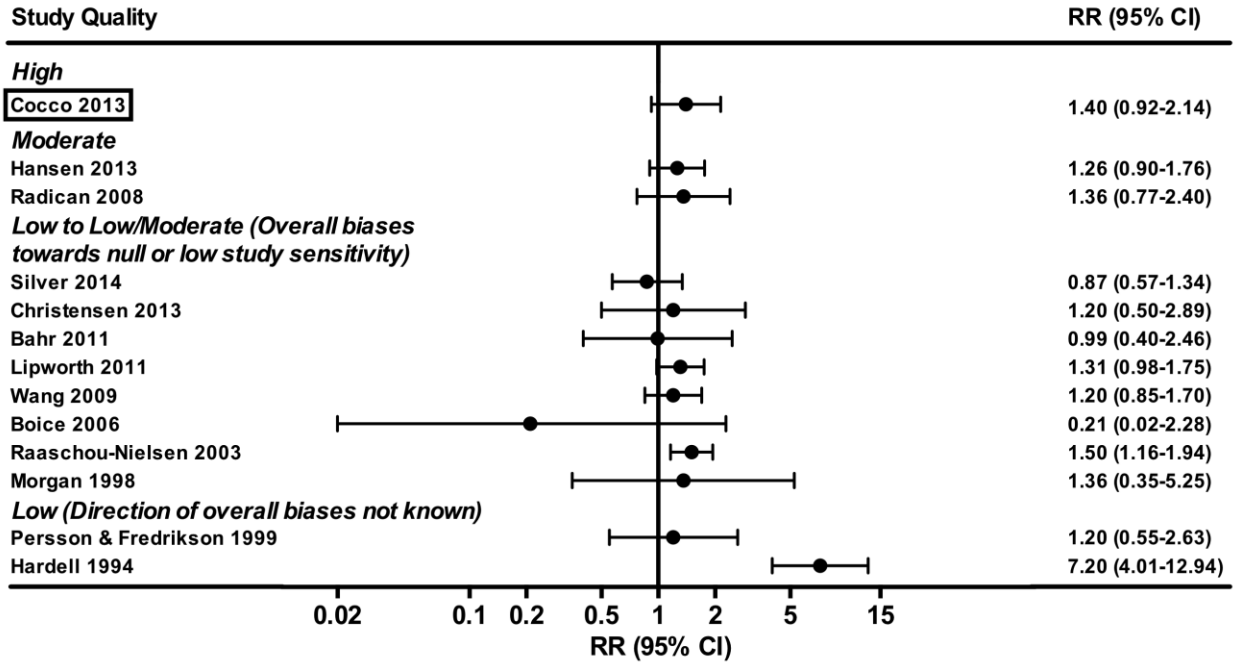
No biases (such as selection) were identified that would bias towards a positive association, although the direction of the biases were not known in the studies by Hardell *et al.* and Persson and Fredrikson (1999). Confounding by other co-exposures can be ruled out reasonably in most of the large case-control studies and the Nordic studies of workers in 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.* (2011a). 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 utility of the studies to inform the cancer hazard evaluation (see Section 3, Appendix D, and Figure 5-1). Studies with low/moderate and low utility were combined into one category. Low utility 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**

An increased risk of NHL and related neoplasms (e.g., follicular lymphoma, multiple myeloma, chronic lymphocytic leukemia) was identified in some epidemiological studies of 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). Although the modes of action of trichloroethylene-induced NHL and related neoplasms are unknown, the key events may be related to effects of trichloroethylene on the immune system. There are also studies in humans and experimental animals that have evaluated the relationship between trichloroethylene and immunotoxicity or markers of immunomodulation. The following sections include a brief review risk factors for NHL (Section 5.2.1) the immune effects of trichloroethylene in humans and experimental animals (Section 5.2.2), possible modes of action for trichloroethylene-induced immune modulation and NHL (Section 5.2.3). Section 5.2.4 summarizes the information..

5.2.1 Risk factors for NHL

Many known risk factors for NHL are related to mechanisms involving chronic antigenic stimulation due to immunomodulation, including autoimmunity and/or immunosupression (Grulich *et al.* 2007, Hardell *et al.* 1998, Ponce *et al.* 2014, Dias and Isenberg 2011, Baecklund *et al.* 2014). 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).

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). 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).

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. Lymphomas can develop from errors arising during the hypermutable stages of B cell development and can arise from either chronic antigenic stimulation (inflammation or autoimmunity) or from impaired pathogen control (immunosuppression). 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). The susceptibility of mature B cells to

oncogenic transformation is due to DNA hypermutation and recombination during immunogen-induced activation and differentiation and results from the increased risk of genetic damage (e.g., double-strand breaks and chromosomal translocations) resulting from these processes during B cell maturation (Baecklund *et al.* 2014, Ponce *et al.* 2014).

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.* 2011, 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) and the cytokines, i.e., interleukins or interferon, that they produce. 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).

5.2.2 Immune effects of trichloroethylene

The effects of trichloroethylene on the immune system have been investigated in humans (Section 5.2.2.1) and experimental animals (Section 5.2.2.2). In addition, some studies have looked at biomarkers for immunomodulation. Of interest is whether changes in these biomarkers are consistent with proposed pathways for lymphoma development.

5.2.2.1 Studies of immunomodulation in humans

This section summarizes the findings of studies (1) reporting risk estimates for autoimmune diseases and trichloroethylene exposure, (2) of trichloroethylene-induced skin hypersensitivity and (3) evaluating the relationship of trichloroethylene and biomarkers of immunomodulation. None of the studies evaluated phenotypic markers that would directly demonstrate immune suppression. The major limitation is they did not examine NHL or other disease.

Studies of trichloroethylene exposure and autoimmune diseases consisted of four case-control studies of systemic sclerosis (sclerodoma) (Diot *et al.* 2002, Garabrant *et al.* 2003, Nietert *et al.* 1998, Marie *et al.* 2014), including one pooled analysis of these studies (Cooper *et al.* 2009), 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 consistent evidence from the body of studies that trichloroethylene exposure is associated with scleroderma for men, but not consistently for women (Diot *et al.* 2002, Garabrant *et al.* 2003, Nietert *et al.* 1998, Marie *et al.* 2014; see Table 5-5). One study found a stronger association of cumulative and maximum intensity exposure to TCE and systemic sclerosis among both men and women who tested positive for anti-Scl-70 autoantibody compared with those who tested negative for the antibody (Nietert *et al.* 1998). The studies have somewhat limited exposure assessments and statistical power due to small numbers of exposed cases to detect an effect of exposure, however. A strength of the studies was that they considered potential demographic or lifestyle confounders. In a pooled analysis of three of the four 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). The data were insufficient to evaluate the findings for undifferentiated connective tissue disease since there was only one exposed case in the only study reporting on this disease (Lacey *et al.* 1999).

Cases of severe generalized dermatitis (i.e., hypersensitivity skin disorders) also were reported among workers in China (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.* 2009) and in Japan, the United States, Canada, and Spain (reviewed by 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, Huang *et al.* 2006; see also review by Watanabe 2011). Cases of idiosyncratic toxic hepatitis have also been reported in Korean workers occupationally exposed to trichloroethylene (see review by Kim and Kim 2010). 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. Although these reports do indicate that exposure to trichloroethylene could be related to the observed immunomodulation, no studies evaluated whether these effects could be linked to NHL.

Studies of trichloroethylene exposure and biomarkers of immunomodulation (e.g., lymphocyte subset populations, antibodies, or other biomarkers of immune function) included both occupational and population-based studies. The occupational studies consisted of a series of studies of trichloroethylene-exposed workers in metalworking and electronic factories in Guangdong province, China (Bassig *et al.* 2013, Hosgood *et al.* 2012, Lan *et al.* 2010, Zhang *et al.* 2013a) and a study in the Italian printing industry (Iavicoli *et al.* 2005). The population studies included two prospective studies 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.

The series of cross-sectional studies of metal and electronics workers in Guangdong province, China, and the Italian study of printing workers conducted the most extensive exposure assessments and provided clear evidence that subjects were exposed to moderate to high levels of trichloroethylene. Studies by Lan *et al.* (2010), Hosgood *et al.* (2012), Bassig *et al.* (2013), and Zhang *et al.* (2013a) were conducted on total lymphocyte and specific subsets. Lan *et al.* (2010) reported that workers exposed to trichloroethylene had dose-related statistically significant lower counts of total lymphocytes, B cells and specific subsets of T lymphocytes (CD4+, CD8+) and

natural killer cells in peripheral blood compared with unexposed controls. A further analysis found significant decreases in CD4+ and CD8 naïve and CD4+ effector memory cells but not other types of CD4+ (central memory) and CD8 (memory) subsets or T cell regulation subsets among trichloroethylene workers compared with controls (Hosgood *et al.* 2012). Trichloroethylene-exposed workers had lower serum levels of IgG, IgM, and lower levels of CD27, and sCD30 cells (members of the TNF receptor family that help regulate cellular activity of T-, B- and natural killer cells) (Lan *et al.* 2010) 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. 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 some evidence of immune modulation associated with trichloroethylene exposure, and possibly with measures of precursors of autoimmunity (e.g., IFN-γ).

Two studies of possible immune effects of trichloroethylene in children and infants were identified but they are of limited utility, in part due to the limited exposure assessment of maternal and child exposure and low reported overall levels of trichloroethylene. The German birth cohort studies of children with atopy (Lehmann *et al.* 2001) potentially exposed to trichloroethylene and other volatile organic compounds reported no association for trichloroethylene exposure and allergies and IL-4 and IFN-γ producing T cells or cytokines. In the study of infants (Lehmann *et al.* 2002), increasing trichloroethylene exposure was associated with a statistically significant decrease in IL-4 producing T cells and non-statistically significant increase in IFN-γ producing T cells but not with IL-2 (in multivariate analysis) or TNF-α producing T cells. An immunosuppressive effect of trichloroethylene is suggested by the significant reduction reported for IL-2-producing T cells in cord blood. However, due to the limited exposure noted above and the correlation of trichloroethylene with other volatile organic compounds and the small number of subjects available for cytokine analysis (in the children's study), no conclusions can be drawn from these studies.

Table 5-5. Case control studies of trichloroethylene exposure and autoimmune diseases in humans[a].

Reference	Study population # cases & controls	Exposure assessment	OR (95% CI); # of exposed cases	Comments
Systemic sclerosis (SSc)				
Nietert *et al.* 1998 South Carolina (USA)	Hospital-based case-control study 178 cases of SSc 200 unmatched clinic controls free of autoimmune and connective tissue disease	Structured interview of self-reported job history (titles, industry, task). Semi-quantitative JEM with expert review to assign scores of intensity and probability of solvents for each job. Cumulative exposure intensity also factored in duration, frequency and calendar year.	Total cases *Cumulative intensity* 2.0 (0.7–5.3); 32 M 1.2 (0.5–2.6); 10 W Maximum intensity 3.3 (1.0-10.3); 30 M 0.9 (0.3-2.3); 6 W Anti-Scl-70[a] SSc cases *Cumulative intensity* 2.6* M; 4.0* W *Maximum intensity* 4.8* M; 0.9 W	Covariates/consideration of confounding: Adjusted for age at disease onset; findings stratified by sex. On average, cases were younger than controls. A greater proportion of cases were women than controls but racial distribution was similar. Strengths: Relatively large study; analysis by multiple matrices of exposure and disease subtypes. Limitations: Limited exposure assessment; no control for possible co-exposures to other solvents and other potential confounders.
Diot *et al.* 2002 France	Hospital-based case-control study 80 cases of SSc 160 matched (age, gender, smoking habits) controls without known autoimmune or chronic interstitial lung disease	Structured interview of self-reported job history (appears self-reported solvent exposures). Semi-quantitative/expert assessment to assign scores for probability, intensity, frequency and duration of exposure for each employment period; cumulative exposure sum of exposure scores for all employment periods.	*Ever vs. never exposure* 4.7 (1.0–21.9); 7 M 2.1 (0.7–6.8); 6 W *High cumulative exposure* 7.6 (1.5–37.4); 7 M + W	Consideration of confounding: Socioeconomic level, professional status, age, sex, and smoking habits similar between cases and controls. No subjects reported history of silicone implants, cosmetic surgery, frequency of hair dyes or drug use (which may be associated with SSc). Strengths: Analysis of high cumulative exposure reduces potential for exposure misclassification. Consideration of potential confounding. Limitations: Limited statistical power for TCE exposure, no adjustment for possible co-exposures to other solvents.

Reference	Study population # cases & controls	Exposure assessment	OR (95% CI); # of exposed cases	Comments
Garabrant *et al.* 2003 Michigan & Ohio (USA)	Population-based case-control study. 660 cases 2,227 matched (race, age, and geographical region) controls without SSc identified by RDD	Structured interview of self-reported job and hobby exposure to 9 solvents and PPE. Self-reported exposure to solvent confirmed by expert review of job history.	Women only *Self reported* 2.0 (0.8-4.8); 8 *Confirmed by expert review* 1.9 (0.6–6.6); 4	Covariates/consideration of confounding: Adjusted for age, race, region, and year of birth. Race/ethnicity, education, marital status, frequency of smoking and alcohol consumption were similar among cases and controls. Current smoking more common in controls and annual income higher in controls Limitations: Potential for exposure misclassification because of limited exposure assessment; small number of exposed cases and controls no control for co-exposures to solvents
Cooper *et al.* 2009	Pooled case-control analysis (Nietert *et al.* 1998, Diot *et al.* 2002, Garabrant *et al.* 2003)	*See individual studies*	2.5 (1.1–5.4) M 1.2 (0.6–2.6) W	Evidence of association with TCE exposure, mostly in men
Marie *et al.* 2014 France	Population-based case-control study 100 cases 300 controls matched (for age, gender and smoking habits) without history of connective tissue disease, systemic vasculitis, other autoimmune systemic disease, cancer, or chronic interstitial lung disease	Structured interview of self-reported job history. Semi-quantitative/expert assessment assignment of probability, intensity, frequency and duration of exposure for each employment period; cumulative exposure based on sum of exposure scores for all employment periods.	Ever exposure 2.8 (0.8–9.4); 8 M 1.4 (0.3–5.4); 4 W *High cumulative exposure (M + W)* 3.6 (1.2–12.09); 8	Consideration of confounding: No differences between cases and controls for age, sex, geographical region, smoking habits, socioeconomic and medical history, including surgeries and drug use which may be related to autoimmune disease, and hair dying Strengths: Analysis of high cumulative exposure reduces potential for exposure misclassification Limitations: Limited statistical power for TCE exposure, no adjustment for possible co-exposures and other confounders

Reference	Study population # cases & controls	Exposure assessment	OR (95% CI); # of exposed cases	Comments
Undifferentiated connective tissue disease				
Lacey *et al.* 1999 Michigan, Ohio (USA) Same design as Garabrant *et al.* 2003	Population-based case-control study Women only 205 cases 2,079 matched (race, age, and geographical region) controls without a medical history of other connective tissue diseases identified by RDD	Same as Garabrant *et al.* 2003	Women only *Self reported* 0.9 (0.1-7.0) 1 cases *Confirmed by expert review* 1.7 (0.2–15.0) 1 case	Covariates/consideration of confounding: Adjusted for age, year of birth. Ethnicity, annual household income, education marital status and smoking frequencies and alcohol use were similar between cases and controls. Limitations: Potential for exposure and disease misclassification. Only one exposed case

* $P < 0.05$.
JEM = job exposure matrix; PPE = personal protective equipment; RRD = random digit dialing.
[a]Auto-antibody.

Table 5-6. Studies of trichloroethylene exposure and lymphocytes, and immune markers in humans[a]

Reference	Study population	Exposure assessment Exposure levels	Findings	Comments
Series of studies of Chinese workers from 6 factories in Guangdong				
Lan *et al.* 2010 Hosgood *et al.* 2012 China	Metal/electronics factory workers Cross-sectional study of healthy workers (excluded those with history of cancer, chemotherapy, and radiotherapy) 80 exposed 96 unexposed (frequency matched by age, sex and region)	Personal air samples 3 weeks prior to blood and urine collection *Mean air (SD)* All: 22.5 (35.9) Low (< 12 ppm): 5.2 (3.5) High (> 12 ppm) 38.4 (44.6)	Exposed vs. non-exposed *Lan* et al. *2010* sCD27[b]: ↓E/R sCD30[b]: ↓E/R Lymphocytes: ↓, E/R NK cells: ↓, E/R B cells: ↓, E/R Total T cells: ↓, E/R CD 4 T cells: ↓ E/R CD 8 T cells: ↓, E/R No differences: WBC, granulocytes, monocytes *Hosgood* et al. *2012* CD 4 and CD 8 Subsets ↓E/R CD 4 naïve CD 4 effector memory CD 8 naïve T subsets: P > 0.05: CD 4 central memory CD 8 central and effector memory Regulatory	Covariates/consideration of confounding: Adjusted for age, sex; (B cells also adjusted for smoking status); smoking status, alcohol consumption, recent infection, and BMI considered in analysis. No differences between exposed and unexposed in smoking status, sex distribution, recent infection and BMI Strengths: Exposure misclassification unlikely because of good exposure assessment; negligible co-exposures to e.g., benzene, styrene, formaldehyde, chlorinated solvents; ability to evaluate exposure-response relationships; healthy participants with no previous cancer, chemotherapy, radiation Limitations: Small study population, cross-sectional design
Bassig *et al.* 2013 China (same population base and design as	Metal/electronics factory workers Cross-sectional 71 exposed 78 unexposed (frequency matched by	Personal air samples (See Lan *et al.* 2010)	*Exposed vs. non-exposed* IL-10: ↓: Controls: ~11 pg/ml < 12 ppm: ~ 3 pg/ml > 12 ppm: ~ 5 pg/ml IL-6: No differences	See Lan *et al.* 2010 Covariates/consideration of confounding: Adjusted for age, sex, total lymphocyte count (Il-10 and TNF-α). Smoking status, BMI and recent infection considered in analysis Strengths: Analyses adjusted for potential

Reference	Study population	Exposure assessment Exposure levels	Findings	Comments
Lan *et al.* 2010)	age, sex and region)		TNF-α: No differences	confounders Limitations: Small study population, cross-sectional design
Zhang *et al.* 2013a China (same population base and design as Lan *et al.* 2010)	Metal/electronics factory workers Cross-sectional 80 exposed 45 unexposed (frequency matched by age, sex and region)	Personal air samples (see Lan *et al.* 2010)	*Exposed vs. non-exposed* IgG: ↓, E/R IgM: ↓ E/R IgE: No differences	See Lan 2010 Covariates/consideration of con Adjusted for age, sex, alcohol use (IgE only). Current smoking, alcohol use, BMI and recent infection considered in analysis. Strengths: Adequate exposure assessment and sample size for immunoglobulin analysis Limitations: Cross-sectional design
Other studies				
Iavicoli *et al.* 2005 Italy	Printing workers/degreasing process Cross-sectional: workers in same factory 35 TCE-exposed workers 30 unexposed factory workers 40 office workers	Assigned to exposure group based on magnitude of TCE exposure (degreasing process) Personal air TCE: exposed workers 35 ± 14 mg/m^3 Urine TCA (mg/g creatinine) Exp. workers: 13.3±5.9 Unexp. workers: 0.02± 0.02 (detection level)	*Exposed vs. non-exposed (factory and office workers*) IL-2: ↑ IL-4: ↓ IFN-γ: ↑	Consideration of confounding: No significant differences in age, smoking habits and residence among the three groups Strengths: Quantitative exposure assessment Limitations: Small, cross-sectional study
Lehmann *et al.* 2002	Infants Longitudinal birth cohort 85 randomly selected infants from study population of ~976	Passive air sampling of VOCs in children's housing over a 4-week period after birth: Median TCE: 0.6 μg/m^3 Maternal exposure questionnaire on sources of exposure	*Cytokine producing cord blood T cells* *Crude data (Mann Whitney U-test)* ↓IL-2 for highest TCE exp. No association for Il-4, IFN-γ, TNF-α	Covariates/consideration of confounding: family atopy history, gender, material smoking during pregnancy Limitations: Limited assessment of TCE and other VOC exposures of infants; measured after cord blood analysis: unclear if investigators blind to cytokine status of

Reference	Study population	Exposure assessment Exposure levels	Findings	Comments
	full-term neonates		Adj. OR for TCE exposure ↑IFN-γ: 3.6 (0.9–14.9): > 75th percentile ↓IL-4: 4.4 (1.1–17.8); < 25th percentile TNF-α and Il-2 No association with ↑ or↓	infants; multiple VOCs were correlated with TCE
Lehmann *et al.* 2001 Germany	3-year old children (atopy risk) LARS (Leipzig Allergy Risk Children's Study) Longitudinal birth cohort 121 3-year olds at risk for atopy (IgE > 0.9kU/l)) with VOC data; cytokines producing T cells on subgroup of 28	Passive air sampling of VOCs in infant bedrooms over a 4-week period at the end of the 3rd year of life. Mean TCE 0.42 μg/m3	*OR for TCE exposure and allergy sensitization (measured by > 75% IgE)* Milk: 0.7 (0.1–3.5) Egg: 1.3 (0.2–9.5) No significant correlation with indoor TCE exposure and IL-4 and IFN-γ producing T cells (CD+3, CD+8, CD+4)	Covariates/consideration of confounding: Family atopy history, passive smoking Limitations: Limited assessment of TCE and other VOC exposures of infants, and multiple VOCs were correlated with TCE. Results of at risk population may not be generalizable to the general population. Small numbers of subject for cytokine analysis

ANCA = antinuclear antibodies; CD = Cluster of differentiation (T cell types); E/R = exposure-response relationship; IFN = interferon; IgG, E, M = immunoglobulin G, E, M; NK = natural killer cells; IL = interleukin; TNF = tumor necrosis factor; VOC = volatile organic compounds. ↓ = statistically significant decrease, ↑ =statistically significant increase.

[a]Case reports, studies of mixed or chlorinated solvents, or ecological studies are excluded.

[b]TNF receptor markers

5.2.2.2 Studies of Immunomodulation in experimental animals

Overall, evidence suggests that exposure to trichloroethylene or its metabolites causes alterations in the immune system, including autoimmune disease, in experimental animals based on studies showing signs of autoimmune disease and/or changes in leukocyte numbers, proliferation, activation, and function (see Table E-4). As explained in more detail in Section 5.2.1, immunomodulation resulting from autoimmunity or immunosuppression leading to continual B cell activation are linked to NHL and could possibly beinvolved in the mode of action for trichloroethylene-induced lymphoma.

Many studies were identified that examined the immunological effects of trichloroethylene in experimental animals. The results for the same endpoint often varied between studies, but these differences might be explained by differences in exposure or by intra- or interspecies variation (e.g., strain of mice, use of rats or dogs). Differences in species, strain, and exposure were considered and are noted in the text below when results differ between studies. 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).

While experimental animal model models do not exist for all human autoimmune diseases (see Section 5.2.2.1), the autoimmune-prone MRL+/+ mice develops many of the features of systemic lupus erythematosus. General signs of autoimmune disease were suggested by changes in antibodies, immune cell activities, and autoimmune hepatitis in MRL+/+ mice and other species and strains of experimental animals 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, cell surface markers for B cell activation (MHC II) and B cell proliferation were not consistently altered and other markers of B cell activation 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 in target organs such as the liver.

The initiation of autoimmune disease from exposure to trichloroethylene or its metabolites may have been caused by the formation of protein adducts with metabolites (dichloroacetyl-protein) and, through increased oxidative stress, with products of lipid peroxidation (malondialdehyde-protein, hydroxynonenal-protein) (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). Protein adducts were found in the serum and liver, and antibodies against these adducts were found in the serum. A

role for formation of trichloroethylene metabolites in these effects is indicated by the finding that inhibition of CYP2E1 by co-exposure with diallyl sulfide prevented the formation of dichloroacetyl-protein adducts and its specific antibodies (Griffin *et al.* 2000c). In addition, decreasing oxidative stress by the enhancement of the 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. Besides autoimmunity, other trichloroethylene-induced immune effects were reported.

Immunomodulatory findings were reported for a number of different organs and endpoints. While immunomodulatory effects can include immunosuppression, direct evidence for this effect was not generally available. Some evidence for a systemic immunomodulatory effect of trichloroethylene was reported from studies showing increased mortality in mice following a bacterial challenge; however, effects on alveolar macrophage phagocytic activity and phagocytic clearance of bacteria were not entirely consistent with the mortality data (Aranyi *et al.* 1986, Selgrade and Gilmour 2010). Immunomodulation was suggested by a decrease in various peripheral blood leukocytes in studies in different species by different routes of administration. These included decreased numbers of leukocytes, lymphocytes, CD4 T cells, CD8 T cells, and B cells in NOD mice exposed via drinking water (Ravel *et al.* 2004), but the effects were observed only at 23 weeks of exposure and no treatment-related function effects were observed for serum cytokine levels. Decreased CD4 T cell numbers were also reported in rats exposed by intradermal injection (Chen *et al.* 2006), but no differences in cytokines (IL-4 and IFNγ) were found. Decreases in both leukocytes and neutrophils were reported in dogs exposed by intratracheal instillation or intravenous injection (Hobara *et al.* 1984); however, the leukocyte count in the latter study reached a minimum 30 minutes after injection and gradually returned toward normal. The only endpoints that decreased in more that one study were the CD4 T-cell numbers and leukocyte numbers. No effect on peripheral blood leukocyte populations was seen in one study testing chloral hydrate in mice.

Possible signs of immunomodulation were observed in specific organs. In the liver, the cytolytic activity of NK cells was decreased (Wright *et al.* 1991); however, mixed results were seen in the spleen and lymph nodes. For the spleen, most studies found no differences with exposure to trichloroethylene or its metabolites, and no differences in experimental design variables of species, strain, or route of exposure were identified that could explain the mixed results in the spleen. Immune effects observed in some of these studies included 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.* 2008). 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. Since there were decreases in leukocytes in the peripheral blood, but no consistent results in the spleen or lymph nodes, it is possible that the effects seen in the blood were the result of leukocyte extravasation into tissue. The data from studies in mice (Ravel *et al.* 2004) and rats (Chen *et al.* 2006) do not give support for either extravasation or decreases in leukocyte numbers since they did not also look at leukocyte numbers in the spleen or lymph nodes. Changes in cytokines however did not similarly decrease along with CD4 and CD8 T cells (Chen 2006, Ravel 2004). Blood leukocyte numbers in the dog studies (Hobara *et al.* 1984) suggest extravasation might be the explanation since the decreases were temporary and occurred for only two hours or less before increasing back towards pre-dose levels.

5.2.3 Possible modes of action for trichloroethylene-induced immune modulation and NHL

As discussed above, trichloroethylene induces immune modulation in humans and laboratory animals with the strongest evidence for autoimmune effects (Boverhof *et al.* 2013, Cooper *et al.* 2009, Rusyn *et al.* 2014, Weinhold 2009). Immune modulation and autoimmunity can lead to chronic inflammation and antigenic stimulation. Only a few studies in humans examined the immunomodulatory effects of trichloroethylene. Most studies in experimental animals used mouse strains that spontaneously develop conditions resembling systemic lupus erythematosus. Since immunomodulation 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 series of Chinese studies generally suggest that trichloroethylene exerts immunomodulatory 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.* 2008, Wang *et al.* 2012a, 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).

5.2.4 Summary

Severe immune dysregulation, whether from immunosuppression, inflammation, or autoimmune disease, is 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 modulation 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.

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 U.S. age-adjusted rates per 100,000 per year (2007 to 2011) are 12.4 (male) and 4.1 (female) for incidence and 8.5 (male) and 3.4 (female) for mortality (SEER 2014d). 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. U.S. rates have been increasing at about 4% per year for the past decade with an overall incidence rate in 1975 of approximately 2.8 per 100,000. Incidence rates in European countries, from which the remaining studies in the evaluation are drawn, appear to be broadly comparable: for example, age-standardized U.K. incidence rates per 100,000 (2011) are approximately 7.0 (male) and 3.1 (female), with an overall rate of 1.5 in 1975, with an increase of approximately 4% per year over the past decade (Cancer Research UK 2014a). As noted, latencies of solid tumors such as liver cancer are generally considered to be longer than for most lymphohematopoietic cancers (e.g. greater than 20 years), although a shorter latency has been reported in association with some exposures (see Howard 2013). Incidence rates start to increase steeply at a somewhat earlier age (40-44 years) than for kidney cancer, particularly among men. 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. Approximately 75% of primary liver cancers are hepatocellular carcinomas, with cholangiocarcinomas forming the bulk of the remainder.

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 elements (such as study sensitivity) 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 and other elements across studies. Figure 6-1 (below) provides an overview of the studies broadly grouped according to their utility to inform the cancer evaluation.

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.

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 Figure 6-1.

Figure 6-1. Study utility ranking: Liver cancer

Moderate Selection bias unlikely for internal analyses Some concern for exposure misclassification Evaluation of E/R Limited study sensitivity; moderate to high exposure level Limited consideration of potential confounders	Hansen 2013 Radican 2008 Morgan 1998
Low/moderate Selection bias possible (except for internal analysis) Some concern for exposure misclassification Limited evaluation of E/R Low study sensitivity (except for RN) Limited consideration of potential confounders	Lipworth 2011 Boice 2006 Raaschou-Nielsen (RN) 2003
Low Selection bias possible, probable or unknown (except Vlaanderen, Bove, Christensen) Considerable concern for exposure misclassification No evaluation of E/R (except Vlaanderen and Bove) Low study sensitivity Limited consideration of potential confounders	Bove 2014 Silver 2014 Vlaanderen 2013 Christensen 2013 Bahr 2011 Ritz 1999 Greenland 1994

Grey: Utility to inform hazard evaluation; light grey – highest. Blue: Overall potential biases towards the null or lower sensitivity; light blue –most sensitive or least biased. Peach: Most potential biases away from the null. Tan: Multiple limitations; overall direction of potential biases unknown or 1 exposed case (for Christensen *et al.* 2013). E/R = exposure-response relationship.

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. 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. Findings from the other studies were null. Two mortality studies (Boice *et al.* 2006, Morgan *et al.* 1998) observed non-statistically significant, small increases in liver cancer, but were based on small numbers of exposed cases; no exposure gradient was observed in the Morgan study. 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) and the drinking water study (Bove *et al.* 2014) reported no increases in risk but both studies had limited exposure assessment, and were relatively young cohorts. 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. 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					
Vlaanderen *et al.* 2013	5 Nordic countries Record linkage of cancer registry with census questionnaire Semi-quantitative JEM M: 14,702 cases cases, 73,510 controls F: 9,194 cases, 45,970 controls	*Cumulative exp.(unit-yrs)* 0 0.04 0.13 0.72 *High exposure group* Cumulative Men Women Intensity × prevalence Men Women		*ICD-7 155* *HR (Incidence)* 1.00 1.03 (0.91–1.16); 340 0.99 (0.90–1.09); 508 1.00 (0.90–1.11); 422 1.01 (0.78–1.31); 69 1.02 (0.72–1.46); 37 1.07 (0.86–1.33); 99 1.12 (0.79–1.59); 38	Low prevalence of exposure (TCE) and exposure levels likely to be low Strengths; long follow-up, large numbers of cases Limitations: Misclassification of exposure likely; JEM had poor sensitivity and did not account for heterogeneity within jobs and over time; TCE exposure correlated with tetrachloroethylene exposure *Null:* No evidence for an association but limited utility
Hansen *et al.* 2013 (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 5,553 (3,776 M, 1,777 F) Biomonitoring (U-TCA)	*All exposed subjects* 0-yr lag 10-yr lag 20-yr lag *U-TCA (mg/L)* < 5 5–25 25–50 >50 P_{trend}	*ICD-7 155: liver + biliary* *SIR* 1.77 (1.24–2.45); 36 1.83 (1.24–2.56); 32 2.09 (1.34–3.11); 24	*ICD-7 155: liver + biliary* *HR incidence (no lag*) 1.00; 16 0.66 (0.31–1.42); 12 0.45 (0.13–1.54); 5 0.63 (0.22–1.68); 3 0.20	Low exposure levels (only 20% exposed to ≥ 20 ppm) and short duration of employment Covariates: Age, sex, calendar period; indirect consideration of smoking and alcohol consumption Strengths: Biomonitoring data; large numbers of workers ever exposed Limitations: Only 2 or 3 U-TCA measurements per individual and unlikely to estimate lifetime or cumulative exposure; low

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
					statistical power for evaluating modest risks; limited ability to evaluate exposure-response relationship *Evidence for a positive association:* Statistically significant, moderately elevated effect estimate for ever exposure; risks increase with increasing lag but not exposure level
Raaschou-Nielsen *et al.* 2003 (Potential overlap with Hansen *et al.* 2013)	Danish blue-collar workers 40,049 M+F (approx. 70% M) Working at TCE company; size of company surrogate for TCE exposure prevalence	*Men (588,047 pyar)* Primary liver (ICD-7 155) Other liver (ICD-7 156) *Women (118,270 pyar)* Primary liver (155) Other liver (156) *Men and women* *Yr. of 1st employment* <u>Women</u> Before 1970 1970–1979 1980 and later <u>Men</u> Before 1970 1970–1979 1980 and later *Duration employment (yrs)* *Men* < 1 1 to 4	*SIR (Total cohort)* 1.1 (0.74–1.64); 27 1.2 (0.73–1.77); 22 2.8 (1.13–5.80); 7 1.1 (0.22–3.23); 3 *Primary liver* 1.28 (0.89–1.8)[ab] 2.5 (0.5–7.3); 3 2.1 (0.2–7.7); 2 5.9 (0.7–21.2); 2 1.5 (0.9–2.4); 17 0.8 (0.3–1.6); 7 0.9 (0.2–2.6); 3 1.3 (0.6–2.5); 9 1.0 (0.5–1.9); 9	NR	Higher levels of TCE prior to 1970 (40–60 ppm); low levels of exposure after that time Covariates: age, sex, calendar year Strengths: Large numbers of exposed cases; subcohort of subjects with higher exposure potential Limitations: Young cohort, possible selection bias of difference in SES, external analysis only Potential for confounding by smoking among women *Limited evidence for a positive association*: Statistically significant elevated risk of primary liver cancer among women; little evidence of exposure-response relationship

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 Women < 1 1 to 4 ≥ 5	1.1 (0.5–2.1); 9 2.8 (0.3–10.); 2 4.1 (1.1–10.5); 4 1.3 (0.0–7.1); 1 No exposure-response pattern for lagged exposure,		
Aerospace and aircraft manufacturing workers					
Lipworth *et al.* 2011 (update of Boice *et al.* 1999)	Burbank (USA) aircraft manufacturing workers 5,443 (approx. 80% M) Qualitative JEM Individual work histories	TCE Ever exposed TCE: years exposed 0 < 1 1–4 5+ P_{trend}	*SMR* *(ICD-9 155+156)* 0.89 (0.57–1.33); 24	*RR mortality* 1.00; 32 0.67 (0.32–1.42); 10 0.69 (0.28–1.71); 6 0.83 (0.36–1.91); 8 0.20	Exposure levels not reported; short exposure duration Covariates: age, date of birth, date of hire, termination date, sex, and race Strengths: Long follow-up Limitations: Evidence of HWE, few exposed deaths in subgroup analysis; likely exposure misclassification; no evaluation of exposure intensity, 70% had exposure to mixed solvents *Null:* No evidence for a positive association but limited utility (limitations mainly towards the null)
Radican *et al.* 2008 (mortality to 2000) Blair *et al.* 1998	Utah (USA) aircraft maintenance workers N = 7,204 (5,153 M, 1,051 F)	Radican *et al.*: *Ever-exposed* *155 +156* *Primary liver: 155.0* *Cum. exp. (unit-yrs) Men*[a]	NR	*ICD-9* *HR mortality* 1.12 (0.57–2.19); 31 1.25 (0.31–4.97); 8 *ICD-9 155+156)*	Estimated exposure: Most workers exposed to low levels (~10 ppm), modest number of workers exposed to higher levels (~100 ppm). Covariates: age, calendar year and

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
(incidence 1973–1990)	Semi-quantitative JEM, individual work histories	All 0–5 5–25 > 25 All 0–5 5–25 > 25 Blair *et al.* 1998 *Cumulative Exp Men* No TCE exposure < 5 units-yr 5–25 units-yr ≥ 25 units-yr		1.36 (0.59–3.11); 28 1.17 (0.45–3.09); 10 1.16 (0.39–3.46); 6 1.72 (0.68–4.38); 12 *Primary liver* 2.72 (0.34–21.88); 8 3.28 (0.37–29.45); 4 0 4.05 (0.45–36.41); 4 *RR (incidence) (ICD-9 155+156)* 0.2 (0.1–2.4); 1 0.6 (0.1–3.1); 3 0.6 (0.1–3.8); 2 1.1 (0.2–4.8); 4	sex Strengths: Adequate semi-quantitative JEM, long follow-up, adequate statistical power for ever exposure Limitations: Potential for exposure misclassification because of missing information for some workers; limited power due to low numbers of higher exposed workers; long follow-up time (45 years) may be past induction time; cannot rule out confounding from other co-exposures *Limited evidence for a positive association*: Statistically non-significant elevated effect estimates for primary liver cancer; some evidence (not significant) for an exposure-response gradient
Boice *et al.* 2006 (overlap with Zhao *et al.* 2005)	Los Angeles (USA) Rocket engine testing workers 1,111 Men Qualitative JEM; Individual work histories	Ever exposed	*SMR (ICD-9 155+156)* 1.28 (0.35–3.27); 4		Exposure occurred during test engine flush, which is likely to be high Covariates: Date of birth, year of hire, pay type (surrogate for SES) and exposure to hydrazine Strengths: Adequate follow up Limitations: Qualitative exposure assessment; few exposed cases *Null:* Small increase in risk but

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
					limited utility
Morgan *et al.* 1998	Arizona (USA) aircraft manufacturing workers N = 4,733 (2,555 M, 2,178 F) Semi-quantitative JEM; individual work history	Ever exposed Cumulative exp. score Low (2,357) High (2,376) Peak (med/high) vs. low/no	*SMR (liver & biliary)* 0.98 (0.36–2.13); 6 1.32 (0.27–3.85); 3 0.78 (0.16–2.28); 3	*RR (mortality)* 1.48 (0.76–2.89); 6[b] 2.12 (0.59–7.66); 3 1.19 (0.34–4.16); 3 0.98 (0.29–3.35); 3	High-exposure jobs were considered to be ≥ 50 ppm Covariates: age at hire, gender (decade of hire considered but no effect) Strengths: Long follow-up and semi-quantitative exposure Limitations: Evidence of a HWE; potential exposure misclassification among low/medium exposure groups; mortality analysis and few exposed cases *Limited evidence of a positive association:* Statistically non-significant, elevated effect estimate (internal analysis); no evidence for exposure-response relationship; based on 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 3,113 TCE exposed Semi-qualitative	5 modified exposure years (exposure duration modified by exposure potential); 10-yr lag		"*liver, biliary and gallbladder"* *HR (at 5 years)* 0.99 (0.50–1.95); NR	Exposure levels NR; only 13.9% of cohort exposed 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

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
	JEM				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 *Null:* No evidence for a positive association but limited utility
Bahr *et al.* 2011	Kentucky (USA) uranium processing workers (gaseous diffusion plant) 5,535 Men	Exp level (rank-ordered) 1 2 3 All		*"Liver & biliary" SRR (mortality)* 1.00 0.34 (0.05–2.07); NR 0.39 (0.08–1.94); NR 0.43 (0.10–1.84); NR	No information on exposure level or number of workers in each exposure category Limitations: Unclear descriptions of methods and findings; limited statistical power; evidence of HWE and survival effect *Null:* No evidence for a positive association but limited utility
Ritz 1999	Ohio (USA) uranium processing workers 2,971 (M)	Low exp. no lag > 2 years > 5 years Moderate exp. no lag > 2 years > 5 years Low exp. 15-yr lag > 2 years > 5 years Moderate exp. 15-yr lag > 2 years	NR	*ICD-9 155+156 RR (mortality)* 0.93 (0.19–4.53); 3 1.90 (0.35–10.3); 3 4.97 (0.48–51.1); 1 8.82 (0.79–98.6); 1 1.16 (0.24–5.60); 3 2.86 (0.48–17.3); 3 5.53 (0.54–56.9); 1	96% workers with low exposure Covariates: Time since 1st hire, pay type, internal radiation, & same chemical different level Strengths: Follow-up adequate Limitations: Low exposure, limited power; selection bias possible Possible residual confounding by radiation

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 years		12.1 (1.03–144); 1	*Limited evidence for a positive association:* Pattern of increasing risk with increasing exposure and lag but based on small numbers
Greenland *et al.* 1994 (nested case-control study)	Massachusetts (USA) electrical manufacturers N = 12 cases (exposed controls NR)	Ever exposure		*ICD-8 155+156* *OR (mortality)* 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 Covariates: Age, date of death, covariates that changed risk estimate by 20% Limitations: Small numbers of cases and controls and short follow-up, possible selection bias, low quality exposure assessment *Null:* No evidence for a positive association but limited utility
Christensen *et al.* 2013 (case-control)	Montreal (Canada) Population- and hospital-exposure	Ever exposure Substantial exposure		*Liver, presume ICD 155* *OR (incidence)* 1.1 (0.1–8.5); 1 2.1 (0.2–18); 1	Number of cases inadequate for evaluation
Environmental exposure					
Bove *et al.* 2014	North Carolina (USA) (Camp Lejeune) Drinking water contamination Ecological exposure assessment 154,932 men and	*TCE in drinking water (μg/L-month)* ≤ 1 > 1–3,100 > 3,100–7,700 > 7,700–39,745		*"Liver and biliary"* *HR (mortality); 10 yr lag* 1.0 (19) 1.02 (0.48–2.15); 12 1.04 (0.47–2.27); 11 0.86 (0.37–1.97); 9	Estimated mean levels (μg/L-month) TCE from water supply = 358.7; overall cumulative exposure = 6,369 (median) and 5,289 (mean); 20% were exposed to levels between 7,700 and 39,745 Covariates: sex, race, rank and education; other variables considered in the model (did not

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
	women				change risk estimates by 10%) include marital status, birth cohort, date of death, duty occupation. Strengths: Large cohort and adequate modeling of exposure Limitations: Young cohort; no information on individual water consumption; potential confounding from other contaminants e.g., tetrachloroethylene *Null:* No evidence for a positive association but limited utility

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.* (2007). The inclusion and exclusion criteria, systematic data extraction, and methods of analysis used in the EPA meta-analysis were identical to those used for meta-analyses of kidney cancer and NHL 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.* 2007	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 in terms of the studies included and the method of analysis. Scott and Jinot (2011) considered each of the studies up to and including 2011 listed in Table 6.1, with the exception of Bahr *et al.* 2011, Lipworth *et al.* 2011, and Ritz 1999. They did, however, included Boice *et al.* (1999), the earlier study followed up by Lipworth. Alexander *et al.* 2007 included each of the studies listed in Table 6.1 up to 2007 except for Zhao *et al.* (2005). The meta-analysis by Scott and Jinot (2011) suggests an overall statistically significant increase in the mRR for combined liver and biliary cancers, but a slight decrease in the mRR for the highest exposed groups was observed. Alexander *et al.* (2007) reported a comparable mRR. These authors 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, contributing 53% of the weight, and reporting twice the number of events as the other contributing studies. Differences in exposure metrics used in the component studies, and small numbers of cases or deaths 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). Studies conducted since 2011 have not observed overall increases in risks or are of limited utility due to limited statistical power or exposure assessments, or other concerns.

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

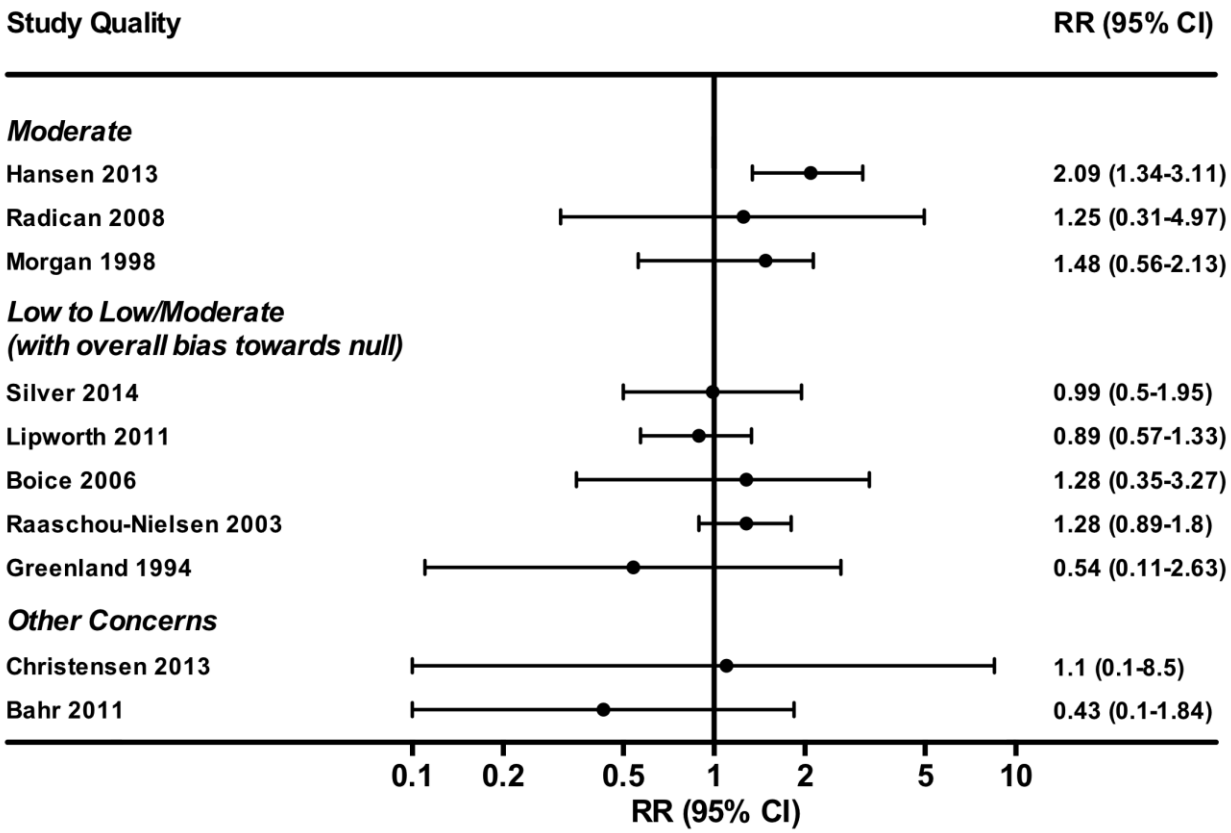
Several individual cohort studies with moderate or low to moderate utility found modest increases in risk of liver cancer (Hansen *et al.* 2013, Raaschou-Nielsen *et al.* 2003, Radican *et al.* 2008, Morgan *et al.* 1998); the strongest evidence was from the external analysis in the updated and pooled 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 utility). 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).

The database is inadequate to evaluate the effect of latency, as few cohort studies conducted lagged vs. unlagged or time since first exposure analyses and data are generally sparse due to limited numbers of cases. SIRS increased with increasing lagged time (no lagged, 10 year lagged, and 20 year lagged) in the Nordic study of biomonitored workers and (Hansen *et al*. 2013). However, no relationship between risk of liver cancer and lagging was obsereved in two other studies (Vlaanderen *et al*. 2013, Raaschou-Nielsen *et al.* 2003). The rest of the studies did not conduct lagged analysis (Christensen *et al.* 2013, Bahr *et al.* 2011, Lipworth *et al.* 2011, Radican *et al.* 2008, Boice *et al*. 2006, Morgan *et al.* 1998) or only reported effect estimates for one lagging period (Bove *et al*. 2014 and Silver *et al.* 2014, Greenland *et al*. 1994).

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 utility 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, Boice *et al*. 2006, 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 (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.* 2007), 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 utility of the study to inform the cancer hazard evaluation (see Section 3, Appendix D and Figure 6-1). Studies with low/moderate and low utility were combined into one category. Low utility 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: modes of action with limited experimental support and modes of action that are inadequately defined or have little to no 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 limited 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). 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. Although the level of evidence varied for the different modes of action, the data were inadequate to support a definite conclusion that any of the proposed modes of action is 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. 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. 2. PPARα activation leads to alterations in cell proliferation and apoptosis. 3. Alterations in cell proliferation and apoptosis cause clonal expansion of initiated cells. 4. Clonal expansion of initiated cells leads to tumor formation.
Oxidative stress	1. Trichloroethylene or its metabolites induce oxidative stress. 2. Oxidative stress leads to chronic inflammation, mutations, and damage to proteins, lipids, and DNA. 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. 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).

Mode of action	Key events
	2. Activation and hepatic infiltration of $CD4^+$ T cells and secretion of inflammatory cytokines. 3. Inhibition of apoptosis in self-reactive $CD4^+$ T cells. 4. Formation of anti-malondialdehyde- and anti-hydroxynonenal-protein adduct antibodies in association with increases in anti-nuclear antibodies. 5. Hepatocyte damage/autoimmune hepatitis. 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). Although there were some differences in the H-*ras* mutation frequencies reported among the studies, the data indicate that trichloroethylene, dichloroacetic acid, and trichloroacetic acid activate mutations in codon 61 of the H-*ras* protooncogene in liver carcinomas of male B6C3F1 mice at a frequency similar to that observed in spontaneous liver tumors. Trichloroacetic acid-induced tumors showed the same mutational spectrum as spontaneous liver tumors; however, trichloroethylene- and dichloroacetic acid-induced tumors had a significant decrease in AAA mutations and a significant increase in CTA mutations compared to spontaneous- or trichloroacetic acid-induced liver tumors. The similarity in frequency and types of H-*ras* mutations in liver tumors induced by trichloroacetic acid compared with spontaneous tumors suggests that trichloroacetic acid may act as a promoter of spontaneous tumors (Eastmond *et al.* 2012). H-*ras* mutations appeared to be a late event because the frequency of H-*ras* mutations increased with time and was higher in hepatocellular carcinomas compared with adenomas (Bull *et al.* 2002). 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. The data also suggest that both trichloroacetic acid and dichloroacetic acid may be involved in trichloroethylene-induced liver

tumors through activation of the H-*ras* protooncogene. However, the mechanisms do not appear to be the same for dichloroacetic acid and trichloroacetic acid (Ferreira-Gonzalez *et al.* 1995).

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, Bull 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 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

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.* 2012a, Wang *et al.* 2013, Wang *et al.* 2009b, Wang *et al.* 2012b). 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

Hepatocellular carcinoma is recognized as a life-threatening complication in the course of autoimmune hepatitis in humans, (Czaja 2013, Nishiyama *et al.* 2004, Watanabe *et al.* 2009, El-Seraf and Rudolph 2007). The primary risk factors for malignant transformation include the presence of cirrhosis at presentation or during treatment and long-term immunosuppressive therapy (Czaja *et al.* 2013). Although the overall frequency of hepatocellular carcinoma in patients with autoimmune hepatitis and cirrhosis ranges from about 1% to 9%, recent clinical data in the United States suggests that the frequency of malignancy in autoimmune hepatitis is comparable with that reported for other types of cirrhosis. Wang and Czaja (1988) reported that the probability of hepatocellular carcinoma in corticosteroid-treated cases of severe autoimmune hepatitis with cirrhosis was 29% after 13 years.

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 inadequate support

Several other modes of action have been proposed for trichloroethylene-induced liver cancer that are incompletely defined or have inadequate 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.* 2012). 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. This monograph focuses on the potential for trichloroethylene exposure to cause kidney cancer, non-Hodgkin lymphoma (NHL), or 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 for carcinogenicity in experimental animals (current listing in the RoC), and reaches a preliminary listing recommendation for trichloroethylene. 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 humans This conclusion is based on epidemiological studies showing that it causes kidney cancer in humans, together with supporting evidence from toxicological, toxicokinetic, and mechanistic studies demonstrating the biological plausibility of its carcinogenicity in humans. Epidemiological studies also provide limited evidence for a causal association for 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 in male rats and lung tumors in mice of both sexes.

The epidemiological, toxicological, toxicokinetic, and mechanistic evidence for kidney cancer, NHL and related cancers, and liver cancer is summarized below.

7.1 Kidney cancer

Epidemiological studies have demonstrated a causal relationship between trichloroethylene exposure and kidney cancer based on consistent evidence of increased risk 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 statistically significant increased risks of kidney cancer across studies combined in two meta-analyses.

Overall, increased risks of kidney cancer were found among individuals with the highest exposure in the most informative studies (i.e., studies with higher levels of exposure to trichloroethylene and 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, non-differential misclassification and lower sensitivity to detect an association (e.g., because of low exposure levels or small numbers of subjects) were concerns in these studies. The meta-analyses also provide strong evidence for an association with kidney cancer. A sensitivity analysis of one meta-analysis 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 by known or suspected occupational 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 the proposed 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, genotoxic, and cytotoxic effects induced by these metabolites in the kidneys. Metabolism of trichloroethylene is qualitative similar in humans and experimental animals. *In vitro* studies in kidney and liver cells from humans and animals have demonstrated the formation of several GST-derived metabolites, some of which (NAcDCVC and DCVG) have been detected in the urine or blood of trichloroethylene-exposed humans and experimental animals. The finding of a significantly elevated risk of renal-cell cancer among trichloroethylene-exposed individuals with a functionally active GSTT1 genotype but not among subjects with a GST-null genotype provides support for the importance of the GSH-conjugation pathway in the carcinogenicity of trichloroethylene in humans.

The available mechanistic data support a mutagenic and cytogenetic mode of action mediated by GSH-conjugated metabolites. These metabolites have been shown to be mutagenic *in vitro* and genotoxic both *in vitro* and *in vivo,* most notably causing damage to human and animal kidney cells *in vitro,* cellular transformation of rat kidney cells *in vitro,* and DNA damage and micronucleus formation in kidney cells from rats exposed *in vivo*. A mechanism potentially contributing to trichloroethylene's carcinogenicity is cytotoxicity and associated regenerative proliferation. Studies in humans also provide evidence that trichloroethylene causes nephrotoxicity, supporting the role of 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 provide limited evidence for a causal association between trichloroethylene exposure and NHL, based on positive associations in several studies and evidence for increased risk of NHL across studies combined in two meta-analyses. The evidence across studies is less consistent than for kidney cancer, and alternative explanations such as chance or confounding cannot reasonably be ruled out.

The strongest evidence for an association between trichloroethylene exposure and NHL comes from the InterLymph pooled analysis (*P* for Fisher's combined probability = 0.004), supported by modest increases in risk in several cohort and case-control studies. The risk of NHL increased with increasing level or duration of exposure in the pooled InterLymph study, one of its component studies, and another case-control study, but evidence for an exposure-response relationship was lacking in several cohort studies. No evidence was found for confounding by lifestyle factors; however, potential confounding by exposure to other solvents, including chlorinated solvents, may have been possible in the aircraft-manufacturing studies.

The mechanisms by which trichloroethylene could cause lymphoma are largely unknown. Immunomodulation, including autoimmunity and immunosuppression, are strongly linked to NHL. There is evidence that trichloroethylene causes immunomodulation in both people and animals, suggesting a biologically plausible role for immunomodulation in induction of NHL by trichloroethylene. It has been proposed that lymphomas can develop from errors arising during the somatic hypermutation phase of B-cell activation, resulting from either chronic antigenic stimulation (autoimmunity) or from 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. 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 has 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 trichloroethylene exposure and liver cancer. A few studies, including two meta-analyses, found modest increases in the risk of liver cancer; however, the findings are inconsistent across studies, and there was little evidence for exposure-response relationships in the individual studies or the meta-analyses. The evidence from recent studies, published since the latest meta-analysis (EPA 2011), appears to be weaker. Most of the studies (both recent and older) had limited ability to detect an association between trichloroethylene exposure and rare cancers such as liver cancer. In addition, the role of chance or confounding by one or more of the common occupational co-exposures or lifestyle factors cannot be completely ruled out.

The mode of action for trichloroethylene-induced liver cancer in mice is unknown but likely is complex, involving key events in several pathways. Studies in experimental animals provide evidence for several potential modes of action resulting primarily from oxidative stress, such as genotoxicity, oxidative damage, peroxisome proliferation, epigenetic events, and autoimmunity (hepatitis). Oxidative metabolites are considered to be more important than GSH-pathway metabolites 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 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 solely by mechanisms that are not relevant to humans.

7.4 Other cancer sites

Although this evaluation focused on kidney cancer, NHL, and liver cancer, authoritative evaluations of the carcinogenicity of trichloroethylene are available for other tissue sites. IARC concluded that although cancer incidence was increased at several other tissue sites, the data were insufficient for an evaluation. Of some interest is cervical cancer, for which statistically significant increased risks were found among women in two of the Nordic cohort studies (the pooled biomonitoring study and the study of blue-collar workers). Excesses of cervical cancer, though not statistically significant, were also observed in the Utah aircraft-manufacturing study and in a case-control study in the Arve Valley area of France, where the screw-cutting industry was prevalent (Charbotel *et al.* 2013). However, the latter study found no association of cervical cancer with cumulative trichloroethylene exposure level or exposure duration. The database for this tissue site is limited by the small number of studies reporting on cervical cancer and the potential for confounding by smoking or human papilloma virus infection.

7.5 Toxicological considerations across end points

The available evidence indicates that trichloroethylene causes genotoxicity, toxicity, and cancer via its metabolic activation to reactive metabolites. Two distinct metabolic pathways for

trichloroethylene have been identified that are common to all mammalian species studied: CYP oxidation and GSH conjugation. As discussed above, 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. The oxidative pathway, primarily through CYP2E1, predominates in all species studied. However, the balance between oxidation and GSH conjugation of trichloroethylene can be altered by genetic polymorphisms or exposure to CYP inducers, and the 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 among study populations in co-exposures or genetic susceptibility factors, both of which could affect the flux through the two metabolic pathways, may explain some of the heterogeneity across studies and cancer end points. Potentially sensitive subpopulations include individuals with GST, CYP2E1, or alcohol dehydrogenase polymorphisms. The frequencies of GSTT1 and GSTM1 polymorphisms vary among ethnic groups, with 40% to 85% of the population having GSTM1- or GSTT1-active genotypes and thus possibly a higher risk of developing cancer from trichloroethylene exposure. (A higher percentage and larger range of GST polymorphisms are found in African populations.) In addition, sex differences in human cancer risk are unclear. Only a few human cancer studies reported risk estimates for specific tissue sites separately for men and women, and several studies included fewer women than men (see Sections 4, 5, 6), limiting the evaluation of potential patterns of sex differences in cancer risk.

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Yale University School of Medicine, CT; University of Sydney, Australia; University of Southern California Keck School of Medicine, CA; University of Leeds, UK; Mayo Clinic College of Medicine, MN; University of Verona, Italy; University of Bristol, UK; University of Washington, WA; Hospital Verge de la Cinta, Spain; Wayne State University, MI.)

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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: α_{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: The 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.

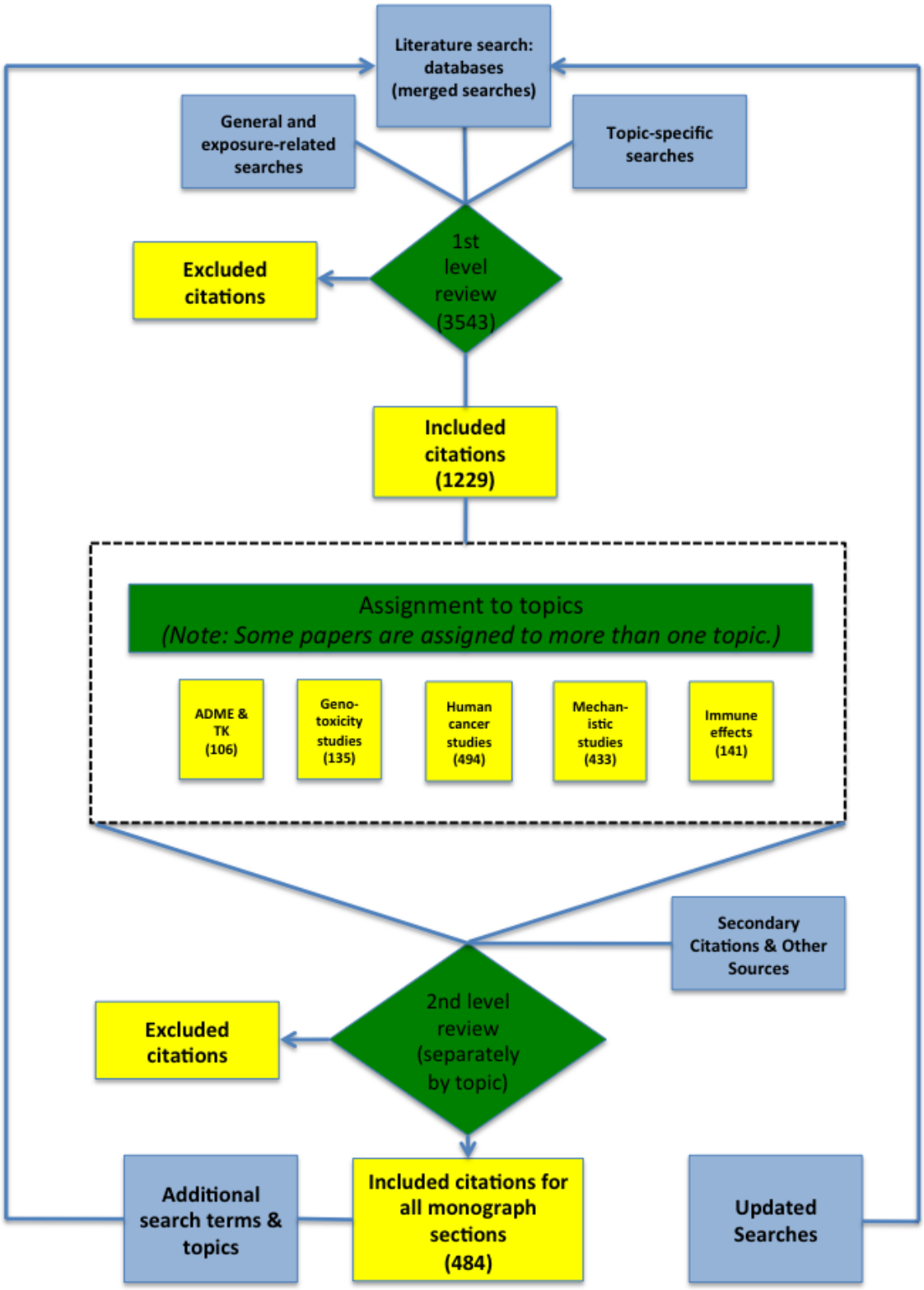
Vapor pressure: The pressure of the vapor over a liquid (and some solids) at equilibrium, usually expressed as mm Hg at a specific temperature (°C).

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. 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 9 4 23	16.7 ± 2.45[c] 30.9 ± 3.3[d] 51.1 ± 3.77[e] 28.3 ± 12.9[f]	1.25 ± 0.81[c] 1.44 ± 0.46[d] 2.77 ± 0.58[e] 1.59 ± 0.84[f]	[74.1 ± 44.1] [47.0 ± 16.0] [54.9 ± 14.1] [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 3	12 ± 3 26 ± 17	0.52 ± 0.17 (males) 0.33 ± 0.15 (females)	48.0 ± 23.1 15.3 ± 10.1	Elfarra *et al.* 1998
Liver microsomes (low affinity)	3 3	93 ± 26 160 ± 162	0.93 ± 0.17 (males) 0.72 ± 0.60 (females)	10.7 ± 3.9 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 3	72 ± 82 42 ± 21	0.96 ± 0.65 (males) 2.91 ± 0.71 (females)	23.8 ± 20.6 80.0 ± 33.9	Elfarra *et al.* 1998
Liver microsomes (low affinity)	5 3	482 ± 104 111 ± 27	2.48 ± 0.97 (males) 4.31 ± 0.31 (females)	5.3 ± 2.2 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 3	378 ± 414 161 ± 29	8.6 ± 4.5 (males) 26.1 ± 7.29 (females)	42.0 ± 28.5 162.8 ± 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 Conjugation	22.1–198 16–47	10–68.4 16–25	0.087–1.12 0.55–1.0
Microsomes (option 1)[b]	Oxidation Conjugation	2.66–11.1 5.9	6.1–111 45	1.71–28.2 7.6
Microsomes (option 2)[b]	Oxidation Conjugation	71–297 157	6.1–111 45	0.064–1.06 0.29
Cytosol (option 1)[c]	Oxidation Conjugation	na 4.5	na 380	na 84
Cytosol (option 2)[c]	Oxidation Conjugation	na 22.7	na 380	na 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 "Genotoxicity 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/did not contain stabilizers.

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

Test system/endpoint	LEC/HIC[a]	Without activation	With activation	Purity, methods and comments[b]	References
S. typhimurium TA100	14,650	–	–	Stabilizers (not epoxides), no DMSO Plate incorporation assay	Henschler *et al.* 1977
S. typhimurium TA100, TA1535	160 (vapor) 2800 (vapor)	– –	(+) –	No stabilizers, no DMSO Dessicator assay; rat and mouse S9 Fro TA100, increased revertants but not doubled; effect greater with mouse S9	Simmon *et al.* 1977
S. typhimurium TA98, TA100	525 (vapor)	– all strains	– all strains	Stabilizers, no DMSO Study conducted in sealed dessicator vials;	Waskell 1978
S. typhimurium TA100, TA1535	160 (vapor) 526 (vapor)	– both strains; both methods	(+) TA100 – TA1535	No stabilizers, ≥ 99.5% purity, no DMSO Two methods: plate incorporation in dessicator and preincubation; rat S9 Increased revertants but not doubled; effect only for plate incorporation in dessicator	Baden *et al.* 1979
S. typhimurium TA100	420 (8% vapor), 16 hr	– plate incorporation	– plate incorporation + preincubation	No stabilizers; purity 99.5%, DMSO used as solvent Two methods: plate incorporation in dessicator and preincubation; mouse S9 Revertants doubled for preincubation assay	Bartsch *et al.* 1979

Test system/endpoint	LEC/HIC[a]	Without activation	With activation	Purity, methods and comments[b]	References
S. typhimurium TA1535		(+)		No stabilizers; purity 99.5%, no DMSO Plate incorporation	Kringstad *et al.* 1981
S. typhimurium TA100	18 (vapor)	–	+	No stabilizers (epoxide-free), no DMSO	Crebelli *et al.* 1982
S. typhimurium TA1535, TA100	50 (vapor)	H: – both strains L: (+) both strains	H: – both strains L: (+) both strains	No stabilizers, purity 99.98% (L) and 99.5% (H); tested high (H, Trichlor 136) and low (L, Trichlor 119) stabilized samples, no DMSO TA100 ±S9 positive only at top dose and 3% survival	Shimada *et al.* 1985
S. typhimurium TA98, TA100, TA1535, TA1537, TA97	167	– all strains	– all strains	No stabilizer; purity >99%, DMSO used as solvent Preincubation assay	Mortelmans *et al.* 1986
S. typhimurium TA1535, TA100, TA1537, TA98	Not reported	+ TA1535, TA100 – TA1537, TA98	+ TA1535, TA100 – TA1537, TA98	Purity not specified (97-99%), no DMSO Dessicator (vapor) assay	Milman *et al.* 1988
S. typhimurium TA98, TA100	1050 (vapor)		–	No stabilizers, purity >99.9%, DMSO used as solvent Dessicator (vapor) assay; S9 from rat and hamster	McGregor *et al.* 1989
S. typhimurium TA98, TA100	1050 (vapor)	–	–	No epoxybutane and epichlorohydrin, oxirane stabilized, purity >99.9%, DMSO used as solvent Preincubation assay	McGregor *et al.* 1989
S. typhimurium TA1535, TA100, TA98	33 (vapor) 130 (vapor) 65 (vapor)	+ TA1535 + TA100 – TA98	+ TA1535 + TA100 – TA98	Stabilizers (epoxybutane and epichlorohydrin and oxirane), DMSO used as solvent Dessicator (vapor) assay	McGregor *et al.* 1989
S. typhimurium BAL13	190 (vapor)	–	–	No stabilizers, purity 99%, DMSO used as solvent Forward mutation assay (ara test)	Roldan-Arjona *et al.* 1991
S. typhimurium YG7108	3,000 µg/plate	+		Purity ≥ 99.5%, DMSO used as solvent CYP E1 metabolically competent strain microcolony assay/revertants	Emmert *et al.* 2006

Test system/endpoint	LEC/HIC[a]	Without activation	With activation	Purity, methods and comments[b]	References
Escherichia coli K12, reverse mutation *arg*$^+$	434	–	+	Purity unknown; analytical grade, no DMSO Reverse mutation (arg$^+$)	Greim *et al.* 1975
Escherichia coli PQ37	13,140	–	–	Purity unknown, use of DMSO unknown SOS chromotest	Von der Hude *et al.* 1988
Escherichia coli PQ37	7,325	–	–	No stabilizers, purity unknown, use of DMSO unknown SOS chromotest	Mersh-Sundermann *et al.* 1989

Sources: EPA 2011a, IARC 2014; if additional detail was needed, primary paper was reviewed.
[a]Treatment concentrations are µg/ml unless noted otherwise. [b]Presence of DMSO in test sample is indicated when noted by authors.
+ = positive, (+) = weak positive, – = negative.

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

Table C-2. *In vitro* genotoxicity studies of trichloroethylene in non-mammalian eukaryotes

Test system/ endpoint	LEC/HIC	Without activation	With activation	Purity, methods and comments[a]	References
Gene mutation					
S. cerevisiae D7	1300	–	+	No stabilizers, solvent corn oil, no DMSO Reverse mutation	Bronzetti *et al.* 1978
S. cerevisiae D7	1970		+	Purity unknown, contained 0.01% thymol as stabilizer, no DMSO Reverse mutation, log phase	Callen *et al.* 1980
S. cerevisiae D7	725	–	(+)	Purity unknown, analytical grade, no DMSO Reverse mutation, log phase and stationary	Koch *et al.* 1988
A. nidulans haploid strain 35	100 ppm (quiescent) 13 ppm (growing)	– +		No stabilizers, purity unknown, no DMSO Forward mutation, dessicator (vapor)	Crebelli *et al.* 1985
Schizosaccharomyces pombe P1	3280 (quiescent) 13,140 (growing)	– –	– –	Measured forward mutation Tested both technical grade and pure (without stabilizers), DMSO (≤ 2%) used as solvent Negative for both sample purities and growth conditions	Rossi *et al.* 1983

Test system/ endpoint	LEC/HIC	Without activation	With activation	Purity, methods and comments[a]	References
Gene conversion					
Saccharomyces cerevisiae	Strain D7: 1970 Strain D4: 2900		+ –	Purity unknown, contained 0.01% thymol as stabilizer, no DMSO Log-phase cultures CYP content 5-fold greater in D7 than D4 Strain D7 had high cytotoxicity at 2900 µg/mL	Callen *et al.* 1980
S. cerevisiae D7	2900	–	–	Purity unknown, analytical grade, no DMSO Stationary and log phase cultures Production of phototropic colonies	Koch *et al.* 1988
S. cerevisiae D7	2600	–	+	No stabilizers, solvent corn oil, no DMSO	Bronzetti *et al.* 1978
Recombination and mitotic crossover					
S. cerevisiae D7	1970		+	Purity unknown, contained 0.01% thymol as stabilizer, no DMSO	Callen *et al.* 1980
Aspergillus nidulans yA2/+ strain 35/17	3660 (quiescent) 90 (growing)	– –		No stabilizers, purity unknown, no DMSO Gene crossover; tested quiescent and growing cells Dessicator (vapor)	Crebelli *et al.* 1985
Mitotic aneuploidy					
S. cerevisiae D61.M	725	+	+	Purity unknown, analytical grade, no DMSO Loss of dominant color homolog	Koch *et al.* 1988

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.
[a]Presence of DMSO in test sample is indicated when noted by authors.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

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

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

Endpoint Test system	LEC/HIC	Without activation	With activation	Purity, methods, and comments[a]	References
Gene mutation					

Endpoint Test system	LEC/HIC	Without activation	With activation	Purity, methods, and comments[a]	References
Mouse lymphoma L5178Y *tk* locus	146 µg/mL	–	+	Purity ≥ 99%, no stabilizers, DMSO used as solvent	Caspary *et al.* 1988
Human lymphoblastoid TK6 cells	600 µg/mL	–	–	Purity ≥ 99%, no stabilizers, DMSO used as solvent	Caspary *et al.* 1988
Micronucleus induction					
Chinese hamster ovary-K_1 cells	150 [0.8–1.4 ppm]	+		Purity 99%, no DMSO Dose-dependent significant increase	Wang *et al.* 2001
Rat primary kidney cells	16.5	+		Purity unknown, reagent grade, solvent EtOH (0.3%) no DMSO Dose-dependent significant increase	Robbiano *et al.* 2004
Human primary kidney cells	16.5	+		Purity unknown, reagent grade, solvent EtOH (0.3%), no DMSO Dose-dependent significant increase	Robbiano *et al.* 2004
Human hepatoma HepG2 cells	0.5 mM [65.7 µg/mL]	+		Purity ≥ 99.5%, DMSO (1%) used as solvent	Hu *et al.* 2008
Human lymphocytes	6 mM	−		Purity unknown, DMSO (0.3%) used as solvent Cytokinesis-block assay	Kumar *et al.* 2009
Chromosomal aberrations					
Chinese hamster lung cells	1000 µg/mL	–	–	Purity unknown, use of DMSO not known	Sofuni *et al.* 1985
Chinese hamster ovary cells	14,900 µg/mL	–	–	No stabilizers, use of DMSO not known but probable	Galloway *et al.* 1987
Human lymphocytes	6 mM	−		Purity unknown, DMSO (0.3%) used as solvent	Kumar *et al.* 2009
Sister chromatid exchange					
Chinese hamster ovary cells	9		–	Purity unknown, no DMSO 1 hr (vapor) Limitations: short exposure time, few doses, no positive control	White *et al.* 1979

Endpoint Test system	LEC/HIC	Without activation	With activation	Purity, methods, and comments[a]	References
Chinese hamster ovary cells	+S9: 401 µg/mL –S9: 700 µg/mL	(+)	+	Purity ≥ 99%, use of DMSO not known but probable	Galloway *et al.* 1987
Human lymphocytes	178 µg/mL	+		No stabilizers, use of DMSO unknown	Gu *et al.* 1981
DNA strand breaks					
Human hepatoma HepG2 cells	0.5 mM [65.7 µg/mL	+		Purity ≥ 99.5 %, DMSO (1%) used as solvent Comet assay	Hu *et al.* 2008
Rat primary kidney cells	16.5	+		Purity unknown (reagent grade), Solvent EtOH (0.3%), no DMSO Comet assay Dose-dependent significant increase	Robbiano *et al.* 2004
Human primary kidney cells	16.5	+		Purity unknown (reagent grade), Solvent EtOH (0.3%), no DMSO Comet assay Dose-dependent significant increase	Robbiano *et al.* 2004
UDS (DNA repair)					
Rat hepatocytes, phenobarbital-induced	368	+		Purity unknown, no DMSO	Costa & Ivanetich 1984
Rat primary hepatocytes	130 (vapor)	– without stabilizers – with stabilizers		Tested samples with and without stabilizers, no DMSO Cytotoxic	Shimada *et al.* 1985
Rat primary hepatocytes	56.77 (without stabilizer) 1445 (with or without stabilizer)	+ without stabilizers – vapor phase testing		No stabiliizers, purity unknown, no DMSO, standard test Tested vapor phase for samples both with and without stabilizers	Williams *et al.* 1989
$B6C3F_1$ mouse primary hepatocytes	NR	+		Stabilizers; purity unknown, no DMSO	Milman *et al.* 1988

Endpoint Test system	LEC/HIC	Without activation	With activation	Purity, methods, and comments[a]	References
Rat primary hepatocytes	NR	–		Stabilizers; purity unknown, no DMSO	Milman *et al.* 1988
Human lymphocytes	2.5 µl/mL	(+)		No stabilizers; purity 97-99%, DMSO (1%) used as solvent	Perocco and Prodi 1981
Cell transformation					
RLV/Fischer rat F1706 embryo cells	144	+		Purity 99.9%, no DMSO	Price *et al.* 1978
Syrian hamster embryo cells	25	(+)		Purity unknown, DMSO used as solvent	Amacher and Zelljadt 1983
BALB/C-3T3 mouse cells	250	(+)		Purity not specified (97-99%), no DMSO	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.
[a]Presence of DMSO in test sample is indicated when noted by authors.
*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 of trichloroethyelne in mammalian cells or rodents

Endpoint/ Test system	LED/HID	Without activation	With activation	Purity, methods and comments[a]	References
In vitro					
Covalent binding Calf thymus DNA	131		+	No stabilizers, purity unknown, no DMSO	DiRenzo *et al.* 1982
Covalent binding Calf thymus DNA	340	–	+	No stabilizers, purity >99%, no DMSO	Bergman 1983
Covalent binding Calf thymus DNA	13		+	No stabilizers, purity >99%, no DMSO	Miller and Guengerich 1983
Covalent binding Rat hepatocyte DNA	13	+		No stabilizers, purity >99%, no DMSO	Miller and Guengerich 1983

Endpoint/ Test system	LED/HID	Without activation	With activation	Purity, methods and comments[a]	References
Covalent binding Mouse hepatocyte DNA	13	+		No stabilizers, purity >99%, no DMSO	Miller and Guengerich 1983
Covalent binding Calf thymus DNA	3.2		+	Purity 98.9%, no DMSO Mediated by phenobarbitone-induced microsomal and/or cytosolic fractions from rat and mouse organs (mainly liver; also kidney, lung, stomach)	Mazzullo *et al.* 1992
Covalent binding DNA Salmon sperm DNA	270	–	+	No stabilizers, purity >99%, no DMSO	Banerjee and Van Duuren 1978
Protein binding Liver, lung, stomach, kidney microsomes Sprague-Dawley, Osborne-Mendel, and Fischer 344 rats (M &F)		+		No stabilizers, purity >99%, no DMSO Sprague-Dawley-rats had higher binding levels than Osborne-Mendel and Fischer 344 rats Binding was greater for males than females in Osborne-Mendel rats but not other strains	Banerjee and Van Duuren 1978
Protein binding Liver, lung, stomach, kidney microsomes $B6C3F_1$ mouse		+		No stabilizers, purity >99%, no DMSO Liver, lung stomach, kidney Binding was greater in mouse than rat (all strains) in same study Binding was greater in male than female mice	Banerjee and Van Duuren 1978
Protein binding Liver and lung microsomes Osborne-Mendel rat		+		No stabilizers, purity >99%, no DMSO Binding to TCE oxide	Miller and Guengerich 1983
Protein binding Liver microsomes $B6C3F_1$ mouse		+		No stabilizers, purity >99%, no DMSO Binding to TCE oxide	Miller and Guengerich 1983
Protein binding Insulin and adrenocorticotropic hormone Rabbit		+		No stabilizers, purity unknown, no DMSO Binding to TCE oxide	Cai and Guengerich 2001
Protein binding		+		No stabilizers, purity >99%, no DMSO	Miller and Guengerich 1983

Endpoint/ Test system	LED/HID	Without activation	With activation	Purity, methods and comments[a]	References
Liver microsomes Human				Binding to TCE oxide	
In vivo					
Protein binding Liver Kidney $B6C3F_1$ mouse (male)	 10 ppm 600 ppm	 + +		Purity > 99.9%, no DMSO Amine stabilized inh. 6 hr (10 or 600 ppm) Measured reactive metabolite Mouse greater binding than rat in same study, for both doses and tissues	Stott *et al.* 1982
Protein binding Liver, kidney Osborne-Mendel rat (male)	 600 ppm	 –		Purity > 99.9%, no DMSO Amine stabilized inh. 6 hr (10 or 600 ppm) Measured reactive metabolite	Stott *et al.* 1982
Covalent binding Liver DNA $B6C3F_1$ mouse (male)	 1200	 ?		Purity > 99.9%, no DMSO Amine stabilized p.o. × 1	Stott *et al.* 1982
Covalent binding Liver, kidney, lung, stomach DNA BALB/c mouse (male)	 0.76	 (+)		Purity 98.9%, no DMSO i.p. × 1	Mazzullo *et al.* 1992
Covalent binding Liver, kidney, lung, stomach DNA Wistar rat (male)	 0.76	 (+)		Purity 98.9%, no DMSO i.p. × 1	Mazzullo *et al.* 1992
Covalent binding Spleen, lung, kidney, pancreas, testis, brain DNA NMRI mouse	 67	 –		No stabilizers, purity >99%, solvent peanut oil, no DMSO i.p. × 5 Metabolic incorporation of ^{14}C into nucleotides was observed; findings for liver inconclusive	Bergman 1983
Covalent binding	67	–		No stabilizers, purity >99%, solvent peanut	Bergman 1983

Endpoint/ Test system	LED/HID	Without activation	With activation	Purity, methods and comments[a]	References
Spleen, lung, liver, kidney, pancreas, testis, brain RNA NMRI mouse				oil, no DMSO i.p. × 5 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*, p.o. = orally, i.p. = intraperitoneal injection in mg/kg bw; inh. = inhalation, doses in ppm.
[a]Presence of DMSO in test sample is indicated when noted by authors.
+ = positive, (+) = weak positive, – = negative, ? = inconclusive.

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

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

Test system/ endpoint	LED/HID[1]	Results	Purity, methods and comments	Reference
Gene mutation				
NMRI-Hans/BGA mouse (male) Dominant lethal	3400	–	No stabilizers, purity 99.5%, no DMSO inh. 24 hr × 1	Slacik-Erben *et al.* 1980
Lac Z transgenic mouse (male and female) Lung, liver, spleen, kidney, testicular germ cells	3144	–	No stabilizers, purity >99%, no DMSO inh. 6 hr/d × 6 d No base changes or small deletions	Douglas *et al.* 1999
Micronucleus induction				
Mouse Bone-marrow erythrocytes	750	+	No stabilizers, use of DMSO unknown p.o. in gum arabic × 2	Duprat and Gradiski 1980
$B6C3F_1$ mouse (male) Bone-marrow erythrocytes	2500	–	No stabilizers, purity not reported, no DMSO i.p. in corn oil × 3	Shelby *et al.* 1993
C57BL/6J mouse (male) Bone marrow erythrocytes	9800	–	No stabilizers, purity >99%, no DMSO inh. 6 hr × 1	Kligerman *et al.* 1994
CD-1 mouse (male)	460	+	Purity not reported, no DMSO	Hrelia *et al.* 1994

Test system/ endpoint	LED/HID[1]	Results	Purity, methods and comments	Reference
Bone-marrow erythrocytes			i.p. in corn oil × 1 Correlated with urinary TCOH	
C57B1/6J mouse (male) Spermatocytes	565	–	No stabilizers, purity ≥99%, no DMSO inh. 6 hr/d × 5 d Spermatids examined	Allen *et al.* 1994
C57BL/6J mouse (male) Splenocytes	9800	–	No stabilizers, purity >99%, no DMSO inh. 6 hr × 1	Kligerman *et al.* 1994
Sprague-Dawley CD rat (male) Bone-marrow erythrocytes	5	+	No stabilizers, purity >99%, no DMSO inh. 6 hr × 1 Dose-related increases from 5 to 5000 ppm; findings confirmed in repeated study of high dose	Kligerman *et al.* 1994
Sprague-Dawley CD rat (male) Bone-marrow erythrocytes	960	–	No stabilizers, purity >99%, no DMSO inh. 6 hr × 4 Authors note concurrent controls were unusually high	Kligerman *et al.* 1994
Sprague-Dawley CD rat (male) Bone marrow erythrocytes	5000	–	Purity 99.97%, no DMSO inh. 6 hr × 1	Wilmer *et al.* 2014
Sprague-Dawley CD rat (male) Peripheral blood lymphocytes	8800	–	No stabilizers, purity >99%, no DMSO inh. 6 hr × 1	Kligerman *et al.* 1994
Sprague-Dawley CD rat (male) Peripheral blood lymphocytes	960	–	No stabilizers, purity >99%, no DMSO inh. 6 hr × 4	Kligerman *et al.* 1994
Sprague-Dawley CD rat (male) Kidney cells	3591	+	Purity unknown, reagent grade, no DMSO p.o. in EtOH × 1	Robbiano *et al.* 2004
Chromosomal aberrations				
C57BL/6J mouse (male) Splenocytes	9800	_	No stabilizers, purity >99%, no DMSO inh. 6 hr × 1	Kligerman *et al.* 1994
Sprague-Dawley CD rat (male) Peripheral blood lymphocytes	8800	_	No stabilizers, purity >99%, no DMSO inh. 6 hr x 1	Kligerman *et al.* 1994
Sprague-Dawley CD rat (male) Peripheral blood lymphocytes	960	_	No stabilizers, purity >99%, no DMSO inh. 6 hr × 4	Kligerman *et al.* 1994

Test system/ endpoint	LED/HID[1]	Results	Purity, methods and comments	Reference
CD-1 mouse Bone-marrow cells	1000	–	Purity unknown, use of DMSO unknown p.o. × 1	Loprieno and Abbondandolo 1980
Sister chromatid exchange				
C57BL/6J mouse (male) Splenocytes	9800	–	No stabilizers, purity >99%, no DMSO inh. 6 hr × 1	Kligerman *et al.* 1994
Sprague-Dawley CD rat (male) Peripheral blood lymphocytes	8800	–	No stabilizers, purity >99%, no DMSO inh. 6 hr × 1	Kligerman *et al.* 1994
Sprague-Dawley CD rat (male) Peripheral blood lymphocytes	960	–	No stabilizers, purity >99%, no DMSO inh. 6 hr × 4	Kligerman *et al.* 1994
DNA single-strand breaks				
$B6C3F_1$ mouse (male) Liver	2000	–	No stabilizers, purity unknown, use of DMSO unknown i.p. × 1	Parchman & Magee 1982
NMRI mouse (male) Kidney, liver, lung	790 1300	+ (kidney, liver) − (lung)	No stabilizers, purity 99.5%, no DMSO Alkaline unwinding i.p. in Tween-80 × 1	Walles 1986
$B6C3F_1$ mouse (male) Liver	1500	+	Purity > 99%, no DMSO DNA single strand breaks Alkaline unwinding p.o. in Tween-80 (1%) × 1	Nelson and Bull 1988
Mouse spot test in (DNA alternations) embryos from treated dams	350	–	No stabilizers, purity 99.5%, no DMSO i.p. × 1	Fahrig 1977
Sprague-Dawley rat (male) Liver	3000	+	Purity > 99%, no DMSO Alkaline unwinding p.o. in Tween-80 (1%) × 1	Nelson and Bull 1988
Sprague-Dawley CD rat (male) Kidney	3591	+	Purity reagent grade, no DMSO Comet assay p.o. in EtOH	Robbiano *et al.* 2004
Sprague-Dawley CD rat (male)	2000 ppm [~10,800	–	Purity 99.5%, no DMSO	Clay *et al.* 2008

Test system/ endpoint	LED/HID[1]	Results	Purity, methods and comments	Reference
Kidney	mg/kg/day[a]]		Comet assay inh. 6 hr × 5	
UDS (DNA repair)				
Fisher 344 rat (male) Primary hepatocytes	1000	–	Purity unknown, no DMSO p.o. corn oil or water × 1	Mirsalis *et al.* 1989
B6C3F$_1$ mouse (male and female) Primary hepatocytes	1000	–	Purity unknown, no DMSO p.o. corn oil or water × 1	Mirsalis *et al.* 1989
CD-1 mouse (male) Primary hepatocytes	1000	–	No stabilizers, no DMSO p.o. in corn oil × 1	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.
[a]Estimated 10,800 mg/kg/day based on the following assumptions: inhalation rate for rats = 73 cm^3/min; body weight (white rat) = 113 g and assuming 100% assumption. (10,748 mg/m^3 x 73 cm^3/min x 1 m^3/1,000,000 cm^3 x 1,440 min/day)/ 0.0113 kg = ~10,800 (EPA 2006). Absorption would most likely be lower at 2,000 ppm, resulting in a lower mg/kg/day dose.

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

Table C-6. Cytogenetic studies in peripheral blood lymphocytes from trichloroethylene-exposed workers

Reference	Population	Exposure Group	Findings	Comments
Rasmussen *et al.* 1988 Denmark	15 metal degreaser workers exposed to TCE > 20 hr/wk 669 controls from population-based study and survey of parents with offspring with stable chromosomal abnormalities in same geographical location	Exposed Controls Exposed Controls Exposed Controls	*CA: breaks* 1.90 (1.22−2.84) 0.85 (0.66−1.08)*** *CA: other* 1.35 (0.79−2.16)*** 0.15 (0.08−0.27) *CA: hyperdiploid* 0.79 (0.38−1.46)* 0.24 (0.15−0.38)	15 workers identified from a total of 116 workers Control population may not be comparable to workers although the large size may reduce any potential selection bias Other chromosomal aberrations include translocations, deletions, and inversions.

Reference	Population	Exposure Group	Findings	Comments
Seiji *et al.* 1990 Japan	38 TCE-exposed (22 M, 16 W) 7 ppm 51 controls (26 M, 25 W) matched on age, sex, smoking habits, and geographical location	*Men* Exposed smoker (8) Control smokers (7) Exposed non-smoker (14) Control non-smoker (19) *Women* Exposed non-smokers (16) Control non-smoker (25)	*SCE* 7.06 ± 1.38** 5.10 ± 1.16 6.46 ± 1.25 5.78 ± 1.64 6.15 ± 1.34 6.25 ± 1 42	Workers TCE synthesis and degreasers 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) No independent effect of smoking
Nagaya *et al.* 1989 Japan	22 TCE-exposed workers (~30 ppm) 22 workers without exposure to solvents and matched on age, and sex, and smoking habits.	Exposed Controls	*SCE* 7.7 ± 1.3 8.0 ± 1.4	Employment duration 0.7−34 years, mean 9.7 years 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 9 controls	Exposed Controls	*SCE* 9.045 ± 4.898 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.
* $P < 0.05$, χ^2-test (Rasmussen *et al.*); ** $P < 0.01$ (*t*-test compared with concurrent male controls for Seiji *et al.*); ***$P < 0.001$, χ^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

AF = fraction of inhaled substance absorbed (default = 1)
BW = Body Weight (kg)
BMI = body mass index
CAREX = CARcinogen Exposure (Canada)
CLL = chronic lymphocytic lymphoma
DLBCL = diffuse large B-cell lymphoma
DMV = Department of Motor Vehicles
EAC = equivalent airborne concentrations (mg/m^3)
EL = exposure length (min)
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
MV = minute volume (mL/min)
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
OD = oral dose (mg/kg)
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
PPE = Personal Protective Equipment
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

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 Cohort: Nordic Occupational Cancer Cohort (NOCCA): 45 years of cancer incidence and follow-up for 15 million people 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 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%) High estimated levels of exposure to TCE were found in shoe and leather industry workers, mechanics, laundry and smelting workers. 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. 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. 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

<table>
<tr><th colspan="2">Hansen et al. 2013</th></tr>
<tr><th>Related References</th><th>Geographic Location</th></tr>
<tr><td>Anttila et al. 1995, Axelson et al. 1978, Axelson et al. 1994, Hansen et al. 2001, Tola et al. 1980</td><td>Sweden, Finland, Denmark</td></tr>
<tr><th colspan="2">Population Characteristics</th></tr>
<tr><th>Exposed Cohort and Ascertainment</th><th>Reference Population</th></tr>
<tr><td rowspan="2">Eligibility criteria: All workers provided with urine TCA monitoring in Sweden (1955–1975), Finland (1965–1982), and Denmark (1947–1989) ≥ 1 U-TCA measurement
Exposed cohort: 5,553 workers (3,776 men; 1,777 women); total 154,778 person-yr of observation
Follow-up: Sweden, 1958–2003; Finland, 1967–2004; Denmark, 1968–2008
Loss to follow-up: 0.1%</td><td>National rates (Sweden, Finland, Denmark)
All-cause and all-cancer mortality/incidence
All-cause incidence (SIR): NR
All-cancer incidence (SIR) = 1.06 (0.99–1.13); 997</td></tr>
<tr><th colspan="2">Study Design and Analytical Methods/ Control for Confounding</th></tr>
<tr><td colspan="2">Pooled and extended analysis of three historical cohort cancer incidence (registry) studies
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).
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.</td></tr>
<tr><th colspan="2">Exposure Data and Information Assessment</th></tr>
<tr><th>Exposure: Levels and Co-Exposures</th><th>Exposure Assessment</th></tr>
<tr><td>Mean/median urine TCA levels (mg/L)[a]
Mean Median % samples > 50 mg/L
Sweden: 28.2 ± 39 13.0 17.7
Finland: 30.3 ± 82 9.2 13.3
Denmark: 39.2 ± 78 15.0 20.7
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
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</td><td>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.
Co-exposures (Finland)
TCA Perc TCE
Urine (μmol/L) 48–53 NR NR
Air (ppm) 6 avg < 50 79 avg
Blood (μmol/L) NR 0.4–0.7 20–25</td></tr>
<tr><th>Assessment of potential confounders</th><th>Disease Assessment</th></tr>
<tr><td>NR</td><td>Personal identification number linked to Central Person Registers to ascertain vital status; linkage to national cancer registries. ICD-7 (modified).</td></tr>
</table>

<table>
<tr><th colspan="2">Raaschou-Nielsen et al. 2003</th></tr>
<tr><th>Related References</th><th>Geographic Location</th></tr>
<tr><td>Raaschou-Nielsen et al. 2001, Raaschou-Nielsen et al. 2002; Note: cohort partly overlaps that of Hansen et al. 2001.</td><td>Denmark</td></tr>
<tr><th colspan="2">Population Characteristics</th></tr>
<tr><th>Exposed Cohort and Ascertainment</th><th>Reference Population</th></tr>
<tr><td rowspan="2">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.
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.
Follow-up: 1968–1997
Loss to follow-up: NR, “Virtually complete”</td><td>Danish population</td></tr>
<tr><td>All-cause and all-cancer mortality/incidence</td></tr>
<tr><td></td><td>All cause incidence (SIR): NR
All-cancer incidence:
SIR: 1.08 (1.04–1.12); 2,620 (men)
SIR: 1.23 (1.14–1.33); 624 (women)</td></tr>
<tr><th colspan="2">Study Design and Analytical Methods/ Control for Confounding</th></tr>
<tr><td colspan="2">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)</td></tr>
<tr><th colspan="2">Exposure Data and Information Assessment</th></tr>
<tr><th>Exposure: Levels and Co-Exposures</th><th>Exposure Assessment</th></tr>
<tr><td>All workers in Danish TCE measurement registry: (Raaschou-Nielsen et al. 2001, 2002)
1960–1964: mean U-TCA = 58 mg/L (21 ppm TCE air)[a]
1960s: mean air TCE = 318 mg/m^3 (59 ppm TCE air)
1980–1985: mean U-TCA = 14 mg/L (5 ppm TCE air) [a]
1980s: mean air TCE = 75 mg/m^3 (14 ppm)
Co-exposures NR, Industries include iron and metal (> 50%), electronics, painting, printing, chemicals, dry cleaning</td><td>Potentially exposed workers identified from Central Population Registry (1968 on) and Danish Pension Fund (compulsory membership since 1964).
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.
No exposure data on individual workers</td></tr>
<tr><th>Assessment: Other Exposures</th><th>Disease Assessment</th></tr>
<tr><td>NR</td><td>Danish Cancer Registry
Modified ICD-7</td></tr>
</table>

<table>
<tr><th colspan="2">Lipworth et al. 2011</th></tr>
<tr><th>Related References</th><th>Geographic Location</th></tr>
<tr><td>Boice et al. 1999 (errata published in Boice and McLaughlin 2001); Marano et al. 2000</td><td>Burbank, CA (USA)</td></tr>
<tr><th colspan="2">Population Characteristics</th></tr>
<tr><th>Exposed Cohort and Ascertainment</th><th>Reference Population</th></tr>
<tr><td rowspan="2">Eligibility criteria: All aircraft manufacturing workers employed ≥ 1 year from 1960
Exposed cohort: 5,443 M+F (180,704 person-yr)
Total cohort: 77,943 Aircraft mfg. workers at Lockheed Martin (Burbank)
Follow-up: 1960–2008 or age 95 (avg 32 yr)
Loss to follow-up: 1.7% total cohort</td><td>California (white workers) and USA (non-white workers)</td></tr>
<tr><td>All-cause and all-cancer mortality/incidence</td></tr>
<tr><td colspan="2">All-cause mortality: SMR: 0.91 (0.88–0.93); 4,070
All-cancer mortality: SMR: 0.92 (0.86–0.97); 986</td></tr>
<tr><th colspan="2">Study Design and Analytical Methods/ Control for Confounding</th></tr>
<tr><td colspan="2">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</td></tr>
<tr><th colspan="2">Exposure Data and Information Assessment</th></tr>
<tr><th>Exposure: Levels and Co-Exposures</th><th>Exposure Assessment</th></tr>
<tr><td>No quantitative exposure assessment
TCE used for vapor degreasing up to 1966, replaced by tetrachloroethylene
Approx. 12% workers with routine TCE exposure, 30% routine or intermittent TCE exposure
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</td><td>Qualitative JEM; Occupational job groups developed by industrial hygienists based on walk-through survey, veteran employee interviews and historical industrial hygiene surveys and reports
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)</td></tr>
<tr><th>Assessment: Other Exposures</th><th>Disease Assessment</th></tr>
<tr><td>NR</td><td>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
Nosologist coded cause of death from death certificates using ICD in use at time of death, underlying cause of death.</td></tr>
</table>

<table>
<tr><th colspan="2">Radican et al. 2008</th></tr>
<tr><th>Related References</th><th>Geographic Location</th></tr>
<tr><td>Spirtas et al. 1991, Stewart et al. 1991, Blair et al. 1998 (mortality and incidence)</td><td>Utah (USA)</td></tr>
<tr><th colspan="2">Population Characteristics</th></tr>
<tr><th>Exposed Cohort and Ascertainment</th><th>Reference Population</th></tr>
<tr><td rowspan="2">Eligibility criteria: employed ≥ 1 year 1952–1956
Exposed cohort: 7,204 (6,153 men, 1,051 women) TCE-exposed workers
Total cohort: 10,730 male and 3,725 female civilian aircraft maintenance workers (at Hill Force military base)
Follow-up: mortality1991–2000; incidence 1973–1990
Loss to follow-up: NR</td><td>USA (mortality; Radican et al. 2008) and Utah cancer registry (Blair et al. 1998)
Non-chemical-exposed workers (internal analysis)</td></tr>
<tr><td>All-cause and all-cancer mortality/incidence
Radican et al. 2008 (internal analysis)
All-cause mortality HR = 1.04 (0.98–1.11); 3,628
All-cancer mortality HR = 1.12 (0.96–1.30); 729</td></tr>
<tr><th colspan="2">Study Design and Analytical Methods/Control for Confounding</th></tr>
<tr><td colspan="2">Historical cohort mortality/incidence study; Internal analyses (External analysis reported for 1990 follow-up for mortality only.)
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.</td></tr>
<tr><th colspan="2">Exposure Data and Information Assessment</th></tr>
<tr><th>Exposure: Level and Co-Exposures</th><th>Exposure Assessment</th></tr>
<tr><td>No quantitative exposure (air) assessment specific for TCE, but air measurements available on vapor degreasing and other solvents. Estimated TCE exposures (ppm) were:
<table>
<tr><th></th><th>Peak</th><th>Low level</th></tr>
<tr><td>1939–54</td><td>600</td><td>10</td></tr>
<tr><td>1955–67</td><td>400</td><td>10</td></tr>
<tr><td>1968–78</td><td>200</td><td>0</td></tr>
<tr><td>1979–83</td><td>0</td><td>0</td></tr>
</table>
Cherrie et al. (2001) 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).
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</td><td>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.
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).</td></tr>
</table>

<table>
<tr><th colspan="2">Boice et al. 2006</th></tr>
<tr><th>Related References</th><th>Geographic Location</th></tr>
<tr><td>Overlaps cohort of Ritz et al. 1999 and Zhao et al. 2005 (see above)</td><td>Los Angeles (USA)</td></tr>
<tr><th colspan="2">Population Characteristics</th></tr>
<tr><th>Exposed Cohort and Ascertainment</th><th>Reference Population</th></tr>
<tr><td rowspan="2">Eligibility criteria: male Rocketdyne rocket engine testing workers employed ≥ 6 months from Jan 1, 1948 on and with adequate work histories and identifying data
Exposed cohort: 1,111 test stand mechanics with any estimated exposure to TCE or hydrazine
Total cohort: 8,372 Rocketdyne Aerospace workers (7,083 M, 1,289 F) at the SSFL facility; 1,651 were test stand mechanics
Follow-up: 1948–1999; ~88% of test stand mechanics were followed for over 20 years.
Loss to follow-up: 0.4% test stand mechanics</td><td>External: US population
Internal: Hourly non-administrative Rocketdyne workers at SSFL and adjacent facilities</td></tr>
<tr><th>All-cause and all-cancer mortality/incidence</th></tr>
<tr><td>All-cause mortality: SMR = 0.87 (0.78–0.96); 391
All-cancer mortality: SMR = 1.00 (0.83–1.19); 121</td></tr>
<tr><th colspan="2">Study Design and Analytical Methods/ Control for Confounding</th></tr>
<tr><td colspan="2">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.</td></tr>
<tr><th colspan="2">Exposure Data and Information Assessment</th></tr>
<tr><th>Exposure: Levels and Co-Exposures</th><th>Exposure Assessment</th></tr>
<tr><td rowspan="2">No quantitative exposure assessment
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). PPE only used in later years.</td><td>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. Did not consider PPE. Comprehensive job history based on dates and job titles used to assign workers to specific test stands.</td></tr>
<tr><td rowspan="2">Co-exposures: hydrazine, mixed solvents, rocket fuels, oxidizers, exhaust gases, other chemicals, radiation
8.4% (N = 121) exposed to both hydrazine and TCE</td><td>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.</td></tr>
<tr><th>Assessment: Other Exposures</th><th>Disease Assessment</th></tr>
<tr><td>Smoking history (pack-yr) among subsample of 600 workers</td><td>SSA, California death index, NDI, state vital records, Pension Benefit Information Files, Medicare and Medicaid Services data, company personnel, pension and retirement records
ICD in use at time of death</td></tr>
</table>

<table>
<tr><th colspan="2">Zhao et al. 2005</th></tr>
<tr><th>Related References</th><th>Geographic Location</th></tr>
<tr><td>Morgenstern et al. 1997, Ritz et al. 1999. Members of cohort also part of separate larger mortality cohort study of Boice et al. 2006.</td><td>Los Angeles, California</td></tr>
<tr><th colspan="2">Population Characteristics</th></tr>
<tr><th>Exposed Cohort and Ascertainment</th><th>Reference Population</th></tr>
<tr><td rowspan="2">Eligibility criteria: Male workers at Rocketdyne aerospace facility 1950–1980 with ≥ 2 years' employment and no radiation exposure
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
Total cohort: 55,000 Rockwell/Rocketdyne aerospace workers
Follow-up: 1950–2001 (mortality)
1988–2000 (incidence)
Average follow-up 29 yrs
Loss to follow-up: < 1% for mortality</td><td>Mortality: US population
Incidence: California and 8 other state incidence rates
Internal analysis: Low TCE exposure category</td></tr>
<tr><td>All-cause and all-cancer mortality/incidence</td></tr>
<tr><td colspan="2">All-cause and all cancer mortality (SMR): NR
All-cause and all cancer incidence (SIR): NR</td></tr>
<tr><th colspan="2">Study Design and Analytical Methods/Control for Confounding</th></tr>
<tr><td colspan="2">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</td></tr>
<tr><th colspan="2">Exposure Data and Information Assessment</th></tr>
<tr><th>Exposure: Levels and Co-Exposures</th><th>Exposure Assessment</th></tr>
<tr><td rowspan="2">Limited quantitative exposure assessment
Co-exposures: hydrazine, PAH, benzene (early years), mineral oil, gasoline, fuel oils</td><td>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.</td></tr>
<tr><td>1% workers missing job description; 3% workers with insufficient job description – exposure imputed from job title</td></tr>
<tr><th>Assessment: Other Exposures</th><th>Disease Assessment</th></tr>
</table>

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 Incidence: California Cancer Registry and 8 other state cancer registries. ICD-O (incidence). Reports all lymphohematopoietic cancers (excluding CLL) only, not NHL

<table>
<tr><th colspan="2">Morgan et al. 1998</th></tr>
<tr><th>Related References</th><th>Geographic Location</th></tr>
<tr><td>Wong and Morgan 1990</td><td>Arizona (USA)</td></tr>
<tr><th colspan="2">Population Characteristics</th></tr>
<tr><th>Exposed Cohort and Ascertainment</th><th>Reference Population</th></tr>
<tr><td rowspan="2">Eligibility criteria: All male and female aircraft manufacturing workers employed ≥ 6 months 1950–1985
Exposed cohort: 4,733 (2,555 men; 2,178 women)
Total cohort: 20,508 aircraft manufacturing workers at the Hughes Aircraft Manufacturing Site
Follow-up: 1950(?)–1993 (approx. 66% followed for > 20 yr)
Loss to follow-up: 0.1% excluded due to missing data (not clear if vital status or other data)</td><td>External analysis: NR (assume U.S. population)
Internal analysis: 11,187 male and 4,588 female unexposed workers; peak exposure – used unexposed and low exposed workers as the reference group.</td></tr>
<tr><th>All-cause and all-cancer mortality/incidence</th></tr>
<tr><td></td><td>All-cause mortality: SMR: 0.84 (0.79–0.90); 917
All-cancer mortality/incidence:
SMR: 0.92 (0.81–1.03); 270</td></tr>
<tr><th colspan="2">Study Design and Analytical Methods/ Control for Confounding</th></tr>
<tr><td colspan="2">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</td></tr>
<tr><th colspan="2">Exposure Data and Information Assessment</th></tr>
<tr><th>Exposure: Levels and Co-Exposures</th><th>Exposure Assessment</th></tr>
<tr><td>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.
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
TCE used for vapor degreasing 1952–1977
Co-exposures: NR</td><td>Semi-quantitative individual JEM based on veteran employees' plus company industrial hygienists' exposure rankings. Jobs classified into no, low, medium, high exposure scores.
Cumulative exposure score (low, high) = exposure category × duration of exposure. Peak exposure = jobs with medium and high exposure.
Medium/low exposures may be misclassified.</td></tr>
<tr><th>Assessment: Other Exposures</th><th>Disease Assessment</th></tr>
<tr><td>NR</td><td>SSA; NDI; State death certificates; ICD-7, 8 or 9 in use at time of death</td></tr>
</table>

<table>
<tr><th colspan="2">Silver et al. 2014</th></tr>
<tr><th>Related References</th><th>Geographic Location</th></tr>
<tr><td>Fleming et al. 2014, Clapp and Hoffman 2008</td><td>New York State, US</td></tr>
<tr><th colspan="2">Population Characteristics</th></tr>
<tr><th>Exposed Cohort and Ascertainment</th><th>Reference Population</th></tr>
<tr><td rowspan="2">Eligibility criteria: Workers with 91 or more days of employment 1969–2001; contract and foreign national workers (or without SSN) excluded
Exposed cohort: 3,113 ever exposed to TCE
Total cohort: 34,494 (24,037 men, 10,457 women) employed a microelectronics business facility; hourly workers = 15,447 M and 8,934 W.
Follow-up: 1969–2009; average 25.7 years (total cohort)
Loss to follow-up: NR</td><td>US mortality rates, NY State mortality rates (excluding New York City)</td></tr>
<tr><td>All-cause and all-cancer mortality/incidence</td></tr>
<tr><td colspan="2">All-cause mortality: SMR (all hourly workers)
M: 0.76 (0.73–0.78) 3571; F: 0.73 (0.68–0.79) 823
All-cancer mortality: SMR (all hourly workers)
M: 0.83 (0.78–0.88) 1005; F: 0.86 (0.76–0.96) 291</td></tr>
<tr><th colspan="2">Study Design and Analytical Methods/ Control for Confounding</th></tr>
<tr><td colspan="2">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.
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.</td></tr>
<tr><th colspan="2">Exposure Data and Information Assessment</th></tr>
<tr><th>Exposure: Levels and Co-Exposures</th><th>Exposure Assessment</th></tr>
<tr><td>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).
Lead, tetrachloroethylene, methylene chloride, methyl chloroform, classes of chlorinated and other hydrocarbons, acids, bases used in plant. Information on co-exposures not reported.</td><td>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.
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.</td></tr>
<tr><th>Assessment: Other Exposures</th><th>Disease Assessment</th></tr>
<tr><td>NR</td><td>State vital records or NDI; ICD code in use at time of death</td></tr>
</table>

<table>
<tr><th colspan="2">Yiin et al. 2009</th></tr>
<tr><th>Related References</th><th>Geographic Location</th></tr>
<tr><td>None</td><td>Tennessee, US</td></tr>
<tr><th colspan="2">Population Characteristics</th></tr>
<tr><th>Exposed Cohort and Ascertainment</th><th>Reference Population</th></tr>
<tr><td rowspan="3">Eligibility criteria: hired before 1985, employed 30 days or longer.
Total cohort: 47,941 Uranium enrichment (gaseous diffusion) plant workers; TCE-exposed NR
Cases: 98 multiple myeloma deaths
Follow-up: 1985–1998
Loss to follow-up: NR</td><td>419 controls (219 deaths) 5:1 controls to cases, matched on age, sex, race
Selected by incidence density sampling from risk set of all workers at risk of mortality from multiple myeloma;</td></tr>
<tr><td>All-cause and all-cancer mortality/incidence</td></tr>
<tr><td>Not applicable</td></tr>
<tr><th colspan="2">Study Design and Analytical Methods/ Control for Confounding</th></tr>
<tr><td colspan="2">Nested case-control mortality study.
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.</td></tr>
<tr><th colspan="2">Exposure Data and Information Assessment</th></tr>
<tr><th>Exposure: Levels and Co-Exposures</th><th>Exposure Assessment</th></tr>
<tr><td rowspan="2">Historical area air monitoring data available but inadequate information (e.g. building work location) to link to employees.
Estimated cumulative exposure levels to TCE (mean); 183.8 cases, and 113.4 controls (units not reported).
Internal and external radiation dose estimated: average cumulative exposure = 0.026 mGy cases, 0.012 mGy controls
Other exposures: Mercury and nickel</td><td>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.</td></tr>
<tr><td>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).</td></tr>
<tr><th>Assessment: Other Exposures</th><th>Disease Assessment</th></tr>
<tr><td>NR</td><td>Source of mortality data NR
ICD-8 203; underlying and contributory cause of death</td></tr>
</table>

<table>
<tr><th colspan="2">Ritz 1999</th></tr>
<tr><th>Related References</th><th>Geographic Location</th></tr>
<tr><td>None</td><td>Ohio (USA)</td></tr>
<tr><th colspan="2">Population Characteristics</th></tr>
<tr><th>Exposed Cohort and Ascertainment</th><th>Reference Population</th></tr>
<tr><td rowspan="2">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)
Exposed cohort: 2,971 (of 3,814 eligible) white male uranium processing workers
Follow-up: 1951–1989; mean length: 31.5 years
Loss to follow-up: NR</td><td>U.S. population; NIOSH-CORPS reference data (Zahm et al. 1992)</td></tr>
<tr><td>All-cause and all-cancer mortality/incidence
Total cohort only: mortality (SMR)
All-cause mortality: 0.84 (0.79–0.90); 1,045 deaths
All-cancer mortality: 1.10 (0.99–1.23) 328 deaths</td></tr>
<tr><th colspan="2">Study Design and Analytical Methods/Control for Confounding</th></tr>
<tr><td colspan="2">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).</td></tr>
<tr><th colspan="2">Exposure Data and Information Assessment</th></tr>
<tr><th>Exposure: Levels and Co-Exposures</th><th>Exposure Assessment</th></tr>
<tr><td>No quantitative exposure assessment
Only 6% of cohort had moderate exposure and no workers had heavy exposure.
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)
287 workers excluded because of missing radiation exposure data.</td><td>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.
Workers classified by estimated exposure level categories (light, moderate, heavy) and exposure duration.</td></tr>
<tr><th>Assessment: Other Exposures</th><th>Disease Assessment</th></tr>
<tr><td>Smoking history available for approx. 20% subsample of workers from 1968; used to indirectly estimate smoking prevalence by exposure status among workforce.</td><td>Social Security Administration (prior to 1979)
National Death Index
Internal analysis: ICD-9 codes</td></tr>
</table>

<table>
<tr><th colspan="2">Henschler et al. 1995</th></tr>
<tr><th>Related References</th><th>Geographic Location</th></tr>
<tr><td>None</td><td>Germany</td></tr>
<tr><th colspan="2">Population Characteristics</th></tr>
<tr><th>Exposed Cohort and Ascertainment</th><th>Reference Population</th></tr>
<tr><td rowspan="2">Eligibility criteria: All workers exposed to TCE ≥ 1 year 1956–1975
Exposed cohort: 169 (of eligible 183) male cardboard manufacturing workers exposed to TCE men (5,188 person-yr)
Total cohort: 169 TCE exposed and 190 unexposed workers (6,100 person-yr); Median age 59 years for exposed and 62 for unexposed
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)
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.</td><td>External analysis: local population (mortality) Danish and German Democratic Republic cancer rates (renal-cell cancer incidence)
Internal analysis: 190 workers in factory not exposed to TCE matched as group for age and physical activity; excluding office workers</td></tr>
<tr><td>All-cause and all-cancer mortality/incidence</td></tr>
<tr><td></td><td>All-cause mortality
Exposed: SMR = 0.68 (0.48–0.93); 50 deaths
Unexposed: SMR = 1.03 (0.77–1.35); 52 deaths
All-cancer mortality:
Exposed: SMR = 0.96 (0.51–1.67); 15 deaths
Unexposed: SMR =1.16 (0.65–1.91): 15 deaths
All cause and all cancer incidence not reported</td></tr>
<tr><th colspan="2">Study Design and Analytical Methods/Control for Confounding</th></tr>
<tr><td colspan="2">Historical cohort mortality and incidence study (renal cancer); external and internal analysis (Mantel-Haenszel test statistics ignoring age stratification)</td></tr>
<tr><th colspan="2">Exposure Data and Information Assessment</th></tr>
<tr><th>Exposure: Levels and Co-Exposures</th><th>Exposure Assessment</th></tr>
<tr><td>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.
Long exposure periods (17.8 months)
TCE used from 1956–1975.
Cardboard machine area cleaned with TCE every 2 weeks for 4–5 hour, open system, and poor ventilation, no protective gloves and presumed high exposure, odor recorded and sweet taste in mouth and adverse effects (headache, dizziness, vertigo).
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.
Other solvents, including halogenated and non-halogenated hydrocarbons, pentachlorophenol, 1,1,1-trichloroethane, tetrachloroethane used in “negligible” amounts compared to TCE from 1967.</td><td>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.
Individual employee questionnaire on job history, tasks, materials used.</td></tr>
</table>

Henschler *et al.* 1995	
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). Incidence: hospital and physician records; Physical examination by abdominal sonography; Renal tumors histologically confirmed.

<table>
<tr><th colspan="2">Greenland et al. 1994</th></tr>
<tr><th>Related References</th><th>Geographic Location</th></tr>
<tr><td>None</td><td>Massachusetts (USA)</td></tr>
<tr><th colspan="2">Population Characteristics</th></tr>
<tr><th>Exposed Cohort and Ascertainment</th><th>Reference Population</th></tr>
<tr><td rowspan="2">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)
Cases: 512 cancer deaths, 15 NHL and Hodgkin lymphoma combined, 12 kidney, 9 liver cancers
Follow-up: Workers who died between 1969–1984
Loss to follow-up: NR</td><td>Controls: 1,202 non-cancer deaths “unrelated to exposures under study” (primarily circulatory (78%), respiratory (10%), injury (6%), and other causes (6%)</td></tr>
<tr><td>All-cause and all-cancer mortality/incidence</td></tr>
<tr><td colspan="2">All-cause mortality: SMR: NR</td></tr>
<tr><th colspan="2">Study Design and Analytical Methods/ Control for Confounding</th></tr>
<tr><td colspan="2">Nested case-control analysis among workers at a plant with death benefit claims
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</td></tr>
<tr><th colspan="2">Exposure Data and Information Assessment</th></tr>
<tr><th>Exposure: Levels and Co-Exposures</th><th>Exposure Assessment</th></tr>
<tr><td>No industrial hygiene data
TCE used 1930–1977
NAS (2006) noted low likelihood of TCE potential exposure among subjects.
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)</td><td>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).</td></tr>
<tr><th>Assessment: Other Exposures</th><th>Disease Assessment</th></tr>
<tr><td>NR</td><td>Death records in company pensions system; subset of death certificate diagnoses for cancers with less than 90% confirmation rate verified using hospital records.
ICDA-8 (combined NHL and Hodgkin lymphomas only)</td></tr>
</table>

<table>
<tr><th colspan="2">Wilcosky et al. 1984</th></tr>
<tr><th>Related References</th><th>Geographic Location</th></tr>
<tr><td>Arp et al. 1983, McMichael et al. 1976, McMichael et al. 1974</td><td>Ohio (USA)</td></tr>
<tr><th colspan="2">Population Characteristics</th></tr>
<tr><th>Exposed Cohort and Ascertainment</th><th>Reference Population</th></tr>
<tr><td rowspan="2">Eligibility criteria (exposed cohort): 6,678 current and retired rubber manufacturing workers 40–84 years old in 1964 exposed to selected solvents > 1 year.
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)
Follow-up: 1964–1974
Loss to follow-up: NR</td><td>Controls: 20% age-stratified sample of cohort</td></tr>
<tr><td>All-cause and all-cancer mortality/incidence
N/A
All-cancer mortality/incidence: N/A
SMR: N/A
SIR: N/A</td></tr>
<tr><th colspan="2">Study Design and Analytical Methods/Control for Confounding</th></tr>
<tr><td colspan="2">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</td></tr>
<tr><th colspan="2">Exposure Data and Information Assessment</th></tr>
<tr><th>Exposure: Levels and Co-Exposures</th><th>Exposure Assessment</th></tr>
<tr><td>No quantitative exposure assessment or industrial hygiene measurements available
Co-exposures: 25 solvents identified in different processes</td><td>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.
Exposure defined as ever/never work in a process area where one or more of 25 solvents (including TCE) authorized for use.</td></tr>
<tr><th>Assessment: Other Exposures</th><th>Disease Assessment</th></tr>
<tr><td>NR</td><td>Death certificates; ICD-8 (coded by nosologist)</td></tr>
</table>

<table>
<tr><th colspan="2">Bove et al. 2014</th></tr>
<tr><th>Related References</th><th>Geographic Location</th></tr>
<tr><td>None</td><td>Camp Lejeune, NC, Camp Pendleton, CA (USA)</td></tr>
<tr><th colspan="2">Population Characteristics</th></tr>
<tr><th>Exposed Cohort and Ascertainment</th><th>Reference Population</th></tr>
<tr><td rowspan="2">Eligibility criteria: All Marine and Navy personnel on active duty and stationed at Camp Lejeune between April 1975–December 1985
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.
Follow-up: 1979–2008
Loss to follow-up: 1.3% Camp Lejeune, 1.5% Camp Pendleton</td><td>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.
“Unexposed cohort”: Camp Pendleton</td></tr>
<tr><td>All-cause and all-cancer mortality/incidence
All-cause mortality: SMR: 0.83 (0.81–0.84); 8,964
All-cancer mortality: SMR: 0.85 (0.80–0.90); 1,078</td></tr>
<tr><th colspan="2">Study Design and Analytical Methods/Control for Confounding</th></tr>
<tr><td colspan="2">Retrospective cohort study using ecological exposure assessment; Two types of analyses:
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.
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.
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.</td></tr>
<tr><th colspan="2">Exposure Data and Information Assessment</th></tr>
<tr><th>Exposure: Levels and Co-Exposures</th><th>Exposure Assessment</th></tr>
<tr><td>Two of the eight drinking water systems at Camp Lejeune were contaminated with solvents based on sampling data from 1980 to 1984.
Tarawa Terrace (TT): Contaminated by off-base dry-cleaning business: Primary contaminant PCE
Estimated mean level (μg/L): TCE 3.1; PCE 75.7
Hadnot Point (HP): Contaminated by on-base sources (underground storage tank, industrial spills): Primary contaminant TCE (up to 1,400 μg/L, ~0.04 ppm air equivalent [b])
Estimated mean levels (μg/L): TCE: 358.7, PCE: 14.7, Vinyl Chloride: 24, Benzene: 5.4
TCE and PCE highly correlated with each other
Overall cumulative exposure, μg/L months (ppm-months[b]), for TCE, mean = 6,369 (0.17); median = 5,289 (0.14); 20% were exposed to levels between 7,700 and 39,745 (0.21 – 1.06)
Potential daily exposure from HP could be as high as 3.6</td><td>TCE and other contaminant levels: Historical reconstruction using historical samples, and modeling based on water fate and distribution modeling.
TT water system served on-base houses and HP mainly served bachelor quarters.
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.
Cumulative exposure (μg/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.</td></tr>
</table>

Bove *et al.* 2014	
mg/day (0.07 ppm [b]) (showering and drinking water).	
Assessment: Other Exposures	***Disease Assessment***
Tetrachloroethylene 1,2-Dichloroethylene Vinyl chloride	Multiple sources (such as Social Security, Death Master File, National Death Index) used to determine vital status.

[a] U-TCA (half-life 100 hrs) is approx. linear with air TCE <375 mg/m^3 (70 ppm), according to formula TCE mg/m^3 = [1.96 x U-TCA (mg/L) – 0.7] (Hansen *et al.* 2001)

[b]Oral dose of TCE in drinking water converted to equivalent of airborne occupational exposure (ppm, 8-hr TWA) assuming average 1.5 L day intake, 70 kg body weight, minute volume for typical 8-hr shift = 10 m^3, according to formula: EAC = (OD x BW)/(MV x AF X EL x 10E-06); 10E-06 = conversion factor (mL to m^3); 1 mg/ m^3 TCE = 0.186 ppm

Table D-2. Study descriptions and methodologies: case-control studies of trichloroethylene exposure and kidney cancer.

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 Intensity and prevalence of occupational exposures have been higher in central and eastern Europe than other industrial areas. Estimated median exposure and interquartile range (IQR) Cumulative exposure (ppm-yr): IQR = 0.77–2.87 for controls, median = 1.95; IQR = 0.83–7.25 for cases 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). 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 exposure, 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. 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. 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

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 1992–2000 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 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). 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. 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 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). 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. 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. Exposure level based on combination of exposure duration and frequency and severity of acute pre-narcotic 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.

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 Exposure prevalence to TCE: ≤ 2% of cancer controls or population controls had substantial exposure and 3% had any exposure. 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, and PPE. Proxy interviews were done for 12% of population controls and 14% of kidney cancer cases. 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: age, SES, ethnicity, interview type (self or proxy), and lifestyle factors (such as smoking, alcohol consumption)	Histologically confirmed

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 Prevalence of substantial TCE exposure was low among cases (4% to 10%) and varied by type of JEM. 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. 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

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 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 Exposure prevalence to TCE very rare; ≤ 2% of cancer controls or population controls had substantial exposure and 3% had any exposure. 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, PPE 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. 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: age, SES, ethnicity, interview type (self or proxy), and lifestyle factors (such as smoking, alcohol consumption)	Histologically confirmed

Cocco *et al.* 2013	
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: 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. Participation rate: see individual studies.
Study Design and Analytical Methods	
Pooled analysis of four case 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. 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) Included in pooled InterLymph analysis: Cocco *et al.* 2013	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 TCE exposure prevalence is low: For B-cell lymphoma, 5% among controls with high confidence of exposure, 2% had high cumulative exposure 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 PPE for exposures of *a priori* concern 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.

Deng *et al.* 2013/Wang *et al.* 2009a	
Related References	**Geographic Location**
Morton *et al.* 2003, Zhang *et al.* 2004	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 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 ICD-O-2, M-9590-9642, 9690-9701, 9740-9750

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. Highest cumulative exposure category > 7,794 ppm 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 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. 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

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. 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) Characteristics (demographics and ever smoking) were similar among cases and controls.	Hospitals ICD-9 MM 203, CLL 204.1

Persson and Fredrikson 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 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 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	Umeå 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. 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 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

Assessment of potential biases and other characteristics

Each primary study was systematically evaluated for its ability to inform the cancer hazard identification using similar questions and guidelines outlined in the protocol (see http://ntp.niehs.nih.gov/NTP/roc/thirteenth/Protocols/TCE_Protocol12-31-13_508.pdf). Studies were evaluated for elements of study quality (potential for biases), study sensitivity, the ability to evaluate exposure-response relationships, and the potential for confounding (See Section 3.3.2). The guidelines describe the ideal methods and design for each study element. Two reviewers evaluated study quality in concert with input from technical advisors and from a public webinar (http://ntp.niehs.nih.gov/go/tcewebinar).

The study quality elements for each individual study that contribute to its ability to inform the cancer hazard evaluation are evaluated and summarized in Tables D-4a (cohort and nested case-control studies), D-5a (kidney and liver cancer case-control studies) and D-6a (NHL case-control studies). These elements include the following: (1) the potential for selection and attrition bias (unlikely, possible or probable), (2) the quality of the exposure and disease assessment (good, adequate, limited to adequate and limited) and the (3) likelihood of and concern for exposure or disease misclassification, and whether such misclassification is considered differential or nondifferential. The general terms used for defining the potential for selection or information bias (exposure and disease misclassification) are as follows:

- Unlikely/minimal: Information from study designs and methodologies indicate that they are close to the ideal study characteristics and the potential for bias is unlikely or minimal. (See below for a description of the ideal characteristics for each specific study element).
- Possible: Study designs or methodologies are close to but less than ideal, recognizing that in observational studies, there is almost always some methodological or informational limitation and thus some potential for certain types of bias.
- Probable: Study designs or methodologies suggest that the potential for a specific type of bias is likely.

In some cases there is insufficient information to evaluate the level of concern. If adequate information is available, each type of bias is also characterized as to whether it is differential or non-differential. Differential (systematic) biases in the selection of study participants or information assessment are related to both exposure and disease status, and have the potential to bias findings in one direction or another, whereas non-differential (random) biases, which are not related to both exposure and disease, tend to reduce the precision of the risk estimates and often bias the findings toward the null. For example, occupational cohort studies may have limited exposure data across exposure groups, increasing the potential for non-differential exposure misclassification, and may also have the potential for a healthy worker (hire or survival) effect, a type of selection bias that tends to bias findings away from finding an effect (if present) in studies where the comparison group comes from the general population.

The presence of a potential bias in a study does not necessarily mean that the findings of the study should be disregarded. For example, the effect of confounding may only account for a small percentage of the magnitude of the risk estimate. Therefore, an important step in the process of evaluating biases is to determine the probable impact of the described biases on study results—that is, the magnitude of distortion and the direction in which each bias is likely to

affect the outcome of interest (if known). The impact of the potential bias or confounding on the study findings is discussed in the cancer hazard assessment (See Sections 4.1, 5.1, 6.1)

Selection bias

Selection or attrition bias was considered unlikely if cohorts or cases and controls represented the same underlying population, there was little or no evidence of a healthy worker hire or survival effect, cases and controls were selected by similar criteria that were not related to trichloroethylene exposure, participation was high and not related to exposure or disease status, and loss to follow-up was low (preferably less than 5%) and similar in both groups.

Quality of exposure assessment and misclassification of exposure

Exposure assessment: A ranking of good was given to studies having many of the follow elements: industrial hygiene or biomonitoring data, individual detailed job-task exposure matrices, job or task descriptions, knowledge of the exposure setting, consideration of frequency, confidence and intensity, expert assessment, and/or calendar period-specific exposure data. It should be noted, for example, that not all job-exposure or job-task exposure matrices are of equal quality; some are based only on generic occupational or industrial categories or codes, rather than information specific for the plant or industry under investigation, and this may result in substantial misclassification of exposure.

The assessment of exposure misclassification is complex and involves multiple factors such as the likelihood that subjects were ever exposed and misclassification of exposure level, and thus labels such as unlikely, possible, or probable, do not adequately capture the complexity of exposure misclassification; thus his study element is evaluated qualitatively rather than by category.

Quality of case ascertainment and disease misclassification

Case ascertainment: A ranking of good was given to studies where multiple or verified sources were used to identify vital status and/or cases/deaths and ascertainment of cases/deaths was complete or close to complete.

Disease misclassification, for each endpoint of concern, is ranked as unlikely, possible, or probable, based on the sensitivity and specificity of the disease diagnosis, i.e., whether cases were histologically confirmed and whether the system of disease classification was based on newer ICD classifications.. The potential for bias in case or death misclassification is typically nondifferential, but can also be differential, i.e., differ by exposure status.

Study sensitivity and exposure-response relationships

The study sensitivity and exposure-response elements evaluated and summarized in Tables D-4b (cohort and nested case-control studies), D-5b (kidney and liver cancer case-control studies) and D-6b (NHL case-control studies). A study's sensitivity is defined as the ability to detect an effect of exposure, which is principally a function of study size (specifically, the numbers of trichloroethylene- exposed subjects in cohort studies or the numbers of trichloroethylene-exposed controls in case-control studies), the length of follow-up and levels of exposure to trichloroethylene. A ranking of good was given to studies having many of the following elements: larger numbers of exposed subjects or cases adequate length of follow-up, high levels

of exposure, long exposure duration, large groups or subgroups with a range of exposures from low/medium to high to permit the evaluation of exposure-response relationships and little concern about exposure misclassification. Factual information on these elements is also presented in these tables. Studies less than ideal were assigned rankings of adequate or limited. The adequacy of data (range of exposure) and methods used to evaluate exposure-response relationships were also evaluated.

Overall ranking of studies

In general, studies given the most weight in the cancer hazard evaluation had the following characteristics:

- little evidence of the potential for selection bias
- adequate to good exposure assessment with little evidence for exposure misclassification
- incidence studies, histologically confirmed case or use of more recent classification codes
- adequate sensitivity (e.g., sufficient power, length of follow-up and adequate levels of exposure) to detect an effect of exposure
- potential confounding is considered minimal
- appropriate methods for evaluating exposure-response relationships

The ranking of study sensitivity considered multiple factors. For example, very low (or uncertain) exposure levels or duration and/or a high probability of exposure misclassification may result in the study being inadequate to evaluate cancer risk despite adequate study size, or a lack of other biases or evidence of potential confounding. Conversely, high exposure levels may partly compensate for smaller study sizes in some studies.

Based on the overall evaluation, studies were broadly grouped according to their ability to inform the cancer hazard evaluation based on the above characteristics, as follows:

- high utility: most elements were ranked as having little concern for biases or misclassification or the quality of the element was ranked as good to adequate
- moderate utility: most elements were ranked as having some concern bias or information misclassification, or the quality of the element was ranked as limited
- low to moderate utility: similar to moderate but lower study sensitivity and somewhat greater concerns for exposure or disease misclassification.
- low utility: considerable concerns about exposure misclassification or systematic biases, and low study sensitivity.

Not all elements may equally affect the overall ability of a given study to inform the evaluation. The quality of the exposure assessment and potential for exposure misclassification was given considerable weight in ranking the studies. In addition, studies with high probability of systematic biases were rated low. The impact of identified biases, in terms of both direction and magnitude, and potential for confounding, is evaluated in the cancer hazard assessment in the light of the study findings (Sections 4, 5, and 6). For example, the potential for selection or participation bias, or confounding does not always negate a positive association, if the observed risk estimate is high.

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 case ascertainment and misclassification of diagnosis
Nordic Studies			
Vlaanderen *et al.* 2013 Cancer registry-based (Nordic Occupational Cohort); Nested case-control analysis 76,130 kidney cancer cases (41% F); 380,650 controls (41% F); 23,896 liver cancer cases (38% F), 119,480 controls (38% F) 1960–90 to 2003–05 Mortality	*Unlikely* Adequate methods (census, cancer registry, population registries) for identifying cohort; Controls matched to cases by age, sex, country. 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. Use of population-wide occupational exposure database may lack precision for individual participants. Exposure misclassification (with respect to whether workers were ever exposed) is a concern, and likely to be considerable, 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* Linkage via cancer registry *Misclassification of diagnosis:* *Possible for NHL, unlikely for kidney and liver.* RCC (histologically confirmed), liver and MM; Diagnosis of NHL based on broad ICD-7 classification that includes several diseases and does not differentiate subtypes.
Hansen *et al.* 2013 Pooled Nordic cohort incidence analysis; 5,553 workers (3,776 men, 1,777 women) Axelson *et al.* 1994, Anttila *et al.*1995, Hansen *et al.* 2001	*Unlikely* Adequate methods to select cohort members. All workers with ≥ 1 urine TCA or air TCE measurement included in cohort. No evidence of HWE. 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. 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	*Case ascertainment*: *Adequate* Cases identified in cancer registries via ID linkage; only 0.1% of the cohort was lost to follow-up. *Misclassification of diagnosis:* *Possible for NHL, unlikely for kidney and liver* Histologically confirmed in Swedish study; Diagnosis of NHL based on

Study and number of TCE-exposed subjects	Selection bias and completeness of follow-up	Quality of exposure assessment and misclassification of exposure	Quality of case ascertainment and misclassification of diagnosis
		(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.	broad ICD-7 classification that includes several diseases and does not differentiate subtypes.
Raaschou-Nielsen *et al.* 2003 Danish TCE blue-collar worker cohort; 40,049 workers approx. 70% men) Record linkage incidence study	*Possible* 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. Loss to follow-up: *Minimal;* authors report follow-up as being virtually complete.	*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. 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, which could attenuate exposure-duration relationships.	*Case ascertainment: Adequate* Cases identified via ID linkage with cancer registry. *Misclassification of diagnosis: Possible for NHL, unlikely for kidney and liver* Diagnosis of NHL based on broad ICD-7 classification includes several diseases and does not differentiate subtypes.
Rocket engine testing or aircraft manufacturing workers			
Lipworth *et al.* 2011 Burbank, CA (USA) aircraft manufacturing workers cohort; 5,443 (approx. 80% male) Mortality Study	*Possible* 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. 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. Exposure misclassification is a concern (non-differential) for all analyses.	*Case ascertainment: Adequate* Multiple sources used to determine vital status *Misclassification of diagnosis: Possible (non-differential) for some tumor sites* NDI using ICD at the time of diagnosis; possible concern for diagnosis of NHL

Study and number of TCE-exposed subjects	Selection bias and completeness of follow-up	Quality of exposure assessment and misclassification of exposure	Quality of case ascertainment and misclassification of diagnosis
			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); Blair *et al.* 1998 (incidence) Utah (USA) aircraft maintenance workers cohort; 7,204 (6,153 men, 1,051 women) Mortality and incidence study	*Unlikely* Adequate methods to select cohort: All workers potentially exposed to TCE included in exposed cohort. Little evidence for HWE Loss to follow-up: Not reported	*Adequate to good:* Semi-quantitative calendar year specific JEM constructed from detailed 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. 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.	*Case ascertainment: Adequate* Use of state vital records and NDI for vital status (missing data NR). *Misclassification of diagnosis:* Possible (non-differential) for some tumor sites in mortality study 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. Potential for missing cases that do not result in death for cancers with long survival (kidney and NHL), which would decrease precision.
Boice *et al.* 2006 Los Angeles (USA) rocket engine testing workers cohort; 1,111 men Mortality study Overlap with Zhao *et al.* 2005 cohort	*Possible for external analyses* 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). 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. The probability of being exposed to TCE is greatest in analyses by test engine flush; however, exposure misclassification is still possible.	*Case ascertainment: Adequate* Use of state vital records and NDI for vital status *Misclassification of diagnosis: Possible (non-differential) for some tumor sites* Death certificate using ICD at the time of diagnosis; possible concern for diagnosis of NHL Potential for missing cases that do not result in death for cancers with

Study and number of TCE-exposed subjects	Selection bias and completeness of follow-up	Quality of exposure assessment and misclassification of exposure	Quality of case ascertainment and misclassification of diagnosis
			long survival (kidney and NHL), which would decrease precision.
Zhao *et al.* 2005 Los Angeles (USA) aerospace workers cohort Mortality; 6,044 men Incidence; 5,049 men	*Unlikely* Adequate methods to select cohort; all workers with potential exposure to TCE included in cohort. 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. 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.	*Case ascertainment: Adequate* NDI for cause of death (missing data NR) and multiple cancer registries used for diagnosis (missing data NR). *Misclassification of diagnosis: Unlikely for incidence* Incidence: ICD-O (extension of ICD-10). Deaths: ICD-9 and 10; Underlying and contributing causes of death
Morgan *et al.* 1998 Arizona USA aircraft manufacturing workers cohort; 4733 (2555 men, 2178 women) Mortality study	*Possible for external analysis* 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. 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). 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* Use of SSA, NDI, or state vital records. Potential for missing cases that do not result in death for cancers with long survival (kidney and NHL), which would decrease precision. *Misclassification of diagnosis: Possible (non-differential) for some tumor sites* 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 case ascertainment and misclassification of diagnosis
Silver *et al.* 2014 New York State (USA) electronics manufacturing workers cohort; 24, 037 men, 10,457 women (total cohort) Mortality study	*Unknown for internal analysis used for TCE-exposed subcohort* 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. Exposure misclassification *(*with respect to whether workers were ever exposed) is a concern (non-differential).	*Case ascertainment: Adequate* Use of appropriate methods (State vital records or National Death Index (NDI)) to ascertain vital status. Young cohort (17% deaths) and potential for missing cases of cancers with long survival (especially kidney and NHL), which would decrease precision *Misclassification of diagnosis:* Possible (non-differential) for some tumor sites Death certificate using ICD code at time of death used; possible concern for diagnosis of NHL
Bahr *et al.* 2011 Kentucky (USA) uranium enrichment workers cohort; 5,535 men Mortality study	*Probable* 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 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 Exposure misclassification (non-differential) is a concern and likely to be substantial.	*Case ascertainment: Unknown* Source and completeness of vital status and cause of death data NR *Misclassification of diagnosis:* Possible (non-differential) for some tumor sites Death certificate using ICD code at time of death used; possible concern for diagnosis of NHL Potential for missing cases of cancers with long survival (kidney and NHL), which would decrease precision.
Yiin *et al.* 2009 Tennessee (USA) Uranium enrichment	*Possible* Cohort selection based on employee roster for all workers employed in gaseous diffusion plant prior to 1985 (plant closing	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	*Misclassification of diagnosis of cases: Possible (non-differential):* Cases of multiple myeloma (underlying and contributory causes of death, ICD 203) identified from

Study and number of TCE-exposed subjects	Selection bias and completeness of follow-up	Quality of exposure assessment and misclassification of exposure	Quality of case ascertainment and misclassification of diagnosis
workers Nested case-control mortality study; 47,941 men and women 114 cases of multiple myeloma (ICD 203)	date) and employed >30 days; cases and controls selected based on availability of uranium dose data (appears complete). Loss to follow-up: NR	and work history data missing information on building/work location. Limited information available on assessment. Exposure misclassification (non-differential) is a concern.	death certificates (no other details reported)
Ritz 1999 Ohio (USA) uranium processing workers cohort; 2972 men Mortality study	*Possible* 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 exposure: Loss to follow up: Not reported.	*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. Exposure misclassification (with respect to whether workers were ever exposed) is a concern (non-differential). Most of the workers in this study had low levels of exposure.	*Case ascertainment: Adequate* Use of appropriate methods (Social Security Administration Records (SSA) or National Death Index (NDI)) to ascertain vital status *Misclassification of diagnosis:* Possible (non-differential) for some tumor sites Death certificate (NDI) using ICDA-8 (external analysis) and ICD-9 (internal analysis); possible concern for diagnosis of NHL Potential for missing cases that do not result in death for cancers with long survival (kidney and NHL) which would decrease precision.
Henschler *et al.* 1995 German cardboard manufacturing cohort; 169 men Incidence & mortality study of kidney cancer	*Probable* 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	*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. 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	*Case ascertainment: Limited* 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 case ascertainment and misclassification of diagnosis
	statistically significant 30% decrease in all cancer mortality. Loss to follow-up: *Minimal;* 8% (refusal, ill-health, or untraced) suggesting most cases and deaths were identified.	intensity is likely to vary among workers. It is 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. *Misclassification of diagnosis: Unlikely for incidence, possible for deaths (but only 2 deaths reported).* 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 Massachusetts (USA) electrical manufacturing workers nested case-control study 15 deaths NHL, 12 kidney cancer, 9 liver cancers (men)	*Probable* 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. 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 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.* Death certificate diagnoses verified using hospital records for subset of deaths. 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 Ohio (USA) rubber manufacturing workers	*Unlikely* 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* 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 case ascertainment and misclassification of diagnosis
nested case-control study; 6,678 (men) 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. 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. Exposure misclassification (non-differential) is a serious concern and likely to be substantial.	possible concern for NHL. Potential for missing cases of cancers with long survival (kidney and NHL), which would decrease precision
Drinking Water Study			
Bove *et al.* 2014 Cohort study (drinking water contamination) Camp Lejeune, NC and Camp Pendleton, CA (USA) 154,932 (C Lejeune) 154,969 (C Pendleton) Mortality Study	*Unlikely* Adequate methods for selecting cohort cohort: All active service personnel eligible 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. 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* Multiple sources used to determine vital status including the NDI Potential for missing cases of cancers with long survival (kidney and NHL), which would decrease precision. *Misclassification of diagnosis: possible for some tumor sites.* Death certificate; underlying and contributing causes; ICD NR; possible concern for NHL

Table D-4b. Cohort studies: Study sensitivity and exposure-response analyses

Study Summary (study sensitivity)	Study size/length of Follow-up	Reported or estimated exposure levels or duration	Exposure-response analyses: dose metrics/range lagging analyses
Nordic studies			
Vlaanderen *et al.* 2013 Cancer registry-based, Nordic countries nested case-control study. *Limited* *Large number of exposed cases and controls; however, exposure levels were very low..*	Large cohort: number of exposed cases: 4145 kidney, 1610 liver, 3607 NHL, 1583 multiple myeloma Follow-up: up to 45 years	Levels not reported. Estimated median exposure (unit-yr)[b] for the cumulative exposure categories: 1st tertile: 0.04 (for liver, kidney, NHL, MM) 2nd tertile: 0.25 (liver), 0.13 (kidney), 0.12 (NHL), 0.13 (MM) 3rd tertile: 0.77 (liver), 0.72 (kidney), 0.72 (NHL), 0.74 (MM) Estimated cumulative levels of exposure based on occupational group (not individual job data). 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. Estimated exposure group[a] for highest cumulative exposure: assumed **low** (uncertain because calculation includes prevalence).	Cumulative exposure (categorical and continuous models) (units-yr[b]) Range not reported; tertiles of estimated cumulative exposure only used to evaluate for exposure-response relationship. Lagging, 0,1, 5, 10 yr
Hansen *et al.* 2013 Pooled Nordic cohort incidence analysis *Limited for high exposure effects* *Large numbers of exposed cases that were ever exposed to TCE but few cases with high exposure (especially liver or NHL); Most of the cohort was exposed to low*	Median size cohort: 5,553 workers; ~ 1000 cancer cases Number of exposed cases: 32 kidney 36 liver, 38 NHL ever exposed; 9 kidney, 3 liver, 4 NHL in highest exposure group 49% total workers with > 30 years of follow-up	Low exposure levels and short exposure duration Estimated TCE ambient levels: 4 ppm (median, Finland), 12 ppm (median, Denmark); > 80% of Swedish study with < 20 ppm Only ~20% of subjects had U-TCA levels > 50 mg/L (~ 20 ppm) Median duration of employment (yr): 5.5	Average U-TCA (mg/L, 4 levels). Range: Appears adequate based on U-TCA in exposure groups Lagging: 0, 10, 20 yr

Study Summary (study sensitivity)	Study size/length of Follow-up	Reported or estimated exposure levels or duration	Exposure-response analyses: dose metrics/range lagging analyses
levels for short time periods.		(Sweden) and 6.3 (Denmark), NR for Finland Estimated exposure group [a] for highest U-TCA exposure group (20 ppm): **moderate.**	
Raaschou-Nielsen *et al.* 2003 Danish TCE blue-collar worker cohort Record linkage incidence study *Adequate in subcohort of higher exposed subjects* *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 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 Median exposures to TCE (ppm) (NAS 2006) 1960-1969: 49 1970–1979: 20 1980–1989: ~ 4 Only 21% of workers began employment before 1970 (highest levels). Only 42% of the cohort was considered to be exposed to TCE. Estimated exposure group [a] for high exposure group (since 1970): **moderate**.	Exposure duration (yrs), year of first employment (crude surrogate for level), company size (surrogate for probability of exposure), lag time. Analysis on presumed higher exposed workers Range: Appears to be wide based on exposure changes over time. Lagging 0-9, 10-20, > 20 yr
Rocket engine or aircraft manufacturing workers			
Lipworth *et al.* 2011 Burbank, CA (USA) aircraft manufacturing workers cohort Mortality study *Limited* *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 *Follow-up* Average 32 years	No information on reported levels 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. 12% of the cohort with potential exposure to TCE Estimated exposure group[a] for longest duration: **low** (includes workers with high and low exposure).	Duration of exposure (yr) Range: limited for duration, highest category 5 years Lagging: no analysis

Study Summary (study sensitivity)	Study size/length of Follow-up	Reported or estimated exposure levels or duration	Exposure-response analyses: dose metrics/range lagging analyses
Radican *et al.* 2008 (mortality update); Blair *et al.* 1998 (incidence) Utah (USA) aircraft maintenance workers cohort Mortality and incidence study *Limited for subgroup analysis* *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 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). 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] Estimated exposure group[a] for highest cumulative exposure: **moderate.**	Cumulative exposure (unit-years) and exposure pattern (peak and intermittent exposure) Range. Appears adequate (categories of exposure ranged up to 25 units-year)
Boice *et al.* 2006 Los Angeles (USA) rocket engine testing workers cohort Mortality study *Limited* *Few exposed deaths but presumably high exposure.*	Small cohort: 1,111 workers; 121 cancer deaths; Exposed deaths: 7 kidney Follow-up: 88% of test mechanics followed for over 20 years	Approx. 58% exposed to TCE during engine flushing/cleaning (high exposure); approx. 42% exposed to TCE during utility cleaning (lower exposure)	Exposure duration (yr) Range: Unknown, only two exposure duration categories Lagging: no analysis
Zhao *et al.* 2005 Los Angeles (USA) aerospace workers cohort Mortality and incidence study *Limited* *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 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. 80% of workers employed before 1970 when exposure levels were high. Intensity estimated to be > 200 ppm for 1970 and 400 to 600 ppm for intensity. Cumulative exposure estimated to range up to 38 ppm-	Cumulative exposure score (ranked categories) lagged and unlagged. Range: Adequate Lagging: 0, 20 yr

Study Summary (study sensitivity)	Study size/length of Follow-up	Reported or estimated exposure levels or duration	Exposure-response analyses: dose metrics/range lagging analyses
		yr[c]. Estimated exposure group[a] for cumulative exposure: **moderate.**	
Morgan *et al.* 1998 Arizona (USA) aircraft manufacturing workers cohort Mortality study *Limited statistical power in overall and subgroup analysis; Some workers with potential for exposure to high levels but number not known*	Median size cohort: 4,733; 270 cancer deaths. Exposed deaths: 8 kidney, 6 liver, 3 NHL Follow-up: not reported	High exposure jobs were considered to be > 50 ppm TCE. Unclear on the number of workers in high exposed jobs Estimated exposure group[a] for highest exposure group (peak/cumulative): **moderate**.	Cumulative exposure score ranked , two levels), peak exposure Range: Not known, but only analyzed low vs. high Lagging: no analysis
Other cohorts			
Silver *et al.* 2014 New York State (USA) electronics manufacturing workers cohort Mortality study *Limited* *Exposure prevalence in total cohort low, # exposed deaths and exposure levels NR Analysis by 1 cumulative exposure score*	Medium size exposed cohort: 3113 ever exposed to TCE. 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 (1 category) Range: Not known Lagging: 10 yr
Bahr *et al.* 2011 Kentucky (USA) uranium enrichment workers cohort Mortality study *Unclear* *Inadequate information to evaluate*	Median size cohort: 5,335 men; 32 NHL deaths 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 (ranked) Range: not known Lagging: no analysis
Yiin *et al.* 2009	Number exposed to TCE unknown	Exposure levels or duration not reported. Mean cumulative exposure in cases 183.8 ±	Average cumulative exposure score

Study Summary (study sensitivity)	Study size/length of Follow-up	Reported or estimated exposure levels or duration	Exposure-response analyses: dose metrics/range lagging analyses
Tennessee (USA) uranium enrichment workers nested case-control study *Limited* *Number of exposed deaths and exposure levels unknown.*	*Follow-up*: NR, minimum of 13 years, analysis lagged 15 years.	668.2 for cases and 113.4 ± 558.3 for controls. Units not reported	(1 category) Range: Wide range of estimated cumulative exposure, No analyses by exposure category. Lagging: 0, 5, 50, 20 yr
Ritz 1999 Ohio (USA) uranium processing workers cohort Mortality study *Limited* *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. *Adequate:* Average 31 years	94% workers have low exposure, only 6% of cohort had moderate exposure and no workers had heavy exposure. 54% were employed for > 5 years	Exposure level (ranked); exposure duration (yrs, 2 categories) Range: limited, most exposed to light work Lagging: 0, 15 yr
Henschler *et al.* 1995 German cardboard manufacturing cohort Renal cancer incidence and mortality study *Adequate for very high exposure effects* *Few numbers of exposed cases but very high exposure levels*	Small cohort: 169; 7 RCC deaths 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 Estimated peak exposures (during machine cleaning were > 2,000 ppm) and sustained long-term exposure exceeding 100 ppm (Cherrie *et al.* 2001) 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 Range not reported Lagging: no analysis
Greenland *et al.* 1994 Massachusetts (USA) electrical manufacturing workers nested case-control study *Limited* *Inadequate to evaluate effects from*	Small studies: 15 deaths NHL, 12 kidney cancer, 9 liver cancers (men) 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 Range: not applicable Lagging: no analysis

Study Summary (study sensitivity)	Study size/length of Follow-up	Reported or estimated exposure levels or duration	Exposure-response analyses: dose metrics/range lagging analyses
moderate or high exposure			
Wilcosky *et al.* 1984 Ohio (USA) rubber manufacturing workers nested case-control study *Limited* *Unclear if workers were exposed to TCE*	Small studies: 14 deaths from lymphosarcoma + reticulosarcoma 9 observed cases of lymphosarcoma + reticulosarcoma in case-control study Follow-up: 10 years	No quantitative exposure assessment or industrial hygiene measurements available; Exposure based on authorized use	Ever vs. never exposed Range: not applicable Lagging: no analysis
Drinking water study			
Bove *et al.* 2014 Cohort studies using an ecological exposure (drinking water contamination) Mortality *Unclear* *Adequate number of cases in cohort, number in subgroups not reported; unclear how to compare with occupational studies due to differences in exposure route.*	Large cohort: 154,932 (Camp Lejeune); 1,008 cancer deaths. 42 kidney, 58 liver, 51 NHL; 11–15 for 3 cancers in high exposure groups Follow-up ranged from 23 to 30 years; however, probably insufficient because it was a young cohort.	Estimated mean levels (µg/L): TCE: 358.7 Overall cumulative exposure (µg/L-months) for TCE, mean 6,369.3 (approx. 0.17 ppm-months), median 5,289 (approx. 0.14 ppm-months), 20% were exposed to levels between 7,700 and 39,745 µg/L-months (0.20 – 1.06 ppm-months). 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 (25 ppm-yr). Estimated exposure group[a:] for cumulative exposure: low (could be moderate, but because of uncertainty about different route, is rated as low.	TCE drinking water levels (µg/L-month) *Range: adequate* Lagging: 10 yr

[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 Participation Rates	TCE exposure assessment: Quality and misclassification	Misclassification of disease
Studies in specific areas with knowledge of local industries.			
Moore *et al.* 2010 Hospital-based, Central and E. Europe 1,097 cases RCC, 1,476 controls 1999–2003	*Possible (direction unclear)* Hospital controls excluded smoking-related diseases *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 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* RCC cases histologically confirmed
Charbotel *et al.* 2006, Charbotel *et al.* 2009 Population-based, France 86 cases RCC, 326 controls 1993–2003	*Unlikely* 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) 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. 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 probability of exposure among the exposed group.	*Unlikely* RCC cases histologically confirmed
Brüning *et al.* 2003 Hospital-based, Germany 134 cases RCC, 401 controls 1992–2000	*Possible* Prevalent cases from different hospital departments (presumably most from the same hospital) than residual controls. Cases and control matched by age and gender. Participation rate high among cases but	*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	*Unlikely* RCC cases histologically confirmed

Study	Selection bias Participation Rates	TCE exposure assessment: Quality and misclassification	Misclassification of disease
	not reported for controls.	been blinded. 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).	
Vamvakas *et al.* 1998 Hospital-based, Germany 58 cases RCC, 84 controls 1987–2002	*Probable (differential)* 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 (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. Participation rate: 87% cases and 75% controls	*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. Potential for recall and interviewer bias (differential, overestimate of risk estimate), especially for reporting symptoms due to a legal investigation; However, estimated exposure levels were very high in this study, which may mitigate this concern.	*Unlikely* RCC cases histologically confirmed
Other studies			
Christensen *et al.*	*Unlikely* for population controls	*Adequate to good:* Detailed interview and expert assessment;	*Unlikely*

Study	Selection bias Participation Rates	TCE exposure assessment: Quality and misclassification	Misclassification of disease
2013 Hospital and population-based, Canada 177 cases RCC, 48 liver cancer cases; 533 population controls, 2299 cancer controls 1975–1985	Cases and cancer controls selected from same hospital and controls randomly from same underlying population using similar inclusion criteria Insufficient data regarding the tissue sites of cancer controls, but < 20% of any given cancer site used. Participation rates were 82% for cancer cases (both cancer cases and controls) and 72% for population controls.	duration, frequency, intensity and confidence assessed; Proxy interviews conducted with 12% to 14% of subjects. 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.	RCC, liver cases histologically confirmed
Pesch *et al.* 2000a Population-based, Germany 935 cases RCC, 4,298 controls 1991–1995	*Unlikely* Cases and controls selected from same population using the same inclusion criteria. 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. 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.	*Unlikely* Most RCC cases histologically confirmed; some sonographically confirmed
Dosemeci *et al.* 1999 Population-based, Minnesota US 438 cases RCC, 687 controls	*Unlikely* Cases identified via state cancer registry and controls randomly selected from the same underlying population using similar inclusion criteria. Participation rate was lower among	*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. Exposure misclassification (non-differential) for ever-exposure to TCE is a concern because of the limited JEM and	*Unlikely* RCC cases histologically confirmed.

Study	Selection bias Participation Rates	TCE exposure assessment: Quality and misclassification	Misclassification of disease
1988–1999	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.	lower probability of exposure.	

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 lagging
Studies in specific areas with knowledge of local industries			
Moore *et al.* 2010 Hospital-based, Central and Eastern Europe 1999–2003 *Adequate* *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 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 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) Duration (years): 1.35 (6.3–26.3 for controls) 19.5 (5.8–31) for cases Estimated exposure group for individuals with highest average exposure: moderate to high.	Ever, cumulative (ppm-yrs), average-intensity (ppm), duration (hours, and years); Separate analyses conducted for all and high confidence exposure assessments (> 40% workers probably or definitely exposed jobs). 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. Lagging: 0, 20 yr
Charbotel *et al.* 2006, Charbotel *et al.* 2009 Population-based, France 1993-2003 *Adequate to good* *Adequate number of subjects exposed to high levels of TCE. May not have adequate statistical power in subgroup analysis but good range in exposure intensity.*	Small study: 86 RCC cases; 326 referents 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 Estimated TCE intensities (ppm) for specific jobs 15–18 for open cold degreasing 120 for jobs near open hot degreasing machines up to 300 ppm for work directly above tank 300–600 for emptying, cleaning and refilling degreasers. Cumulative exposure categories: low 1–	Ever exposed, cumulative exposure (ranked), and combined cumulative and peak exposure, trend analysis Range: good (see previous column) Lagging: no analysis

Study Summary	Study size/Exposure prevalence	Reported or estimated exposure levels or duration	Exposure response analyses: Dose metrics /range lagging
		150 ppm-yr, medium 155–335 ppm-yr and > 335 ppm-yr Estimated exposure group[a] for highest cumulative exposure: very high	
Brüning *et al.* 2003 Hospital-based, Germany 1992–2000 *Adequate to good* *Adequate number of subjects exposed to high levels of TCE*	Small/medium study: 134 RCC cases/401 controls Exposure prevalence: 18.7% (N = 25) cases, 9.5% (N = 38) using self assessment 87% cases, 79% controls using CAREX (less confidence)	Very high exposure and long exposures Estimated to be 400–600 ppm during peak (hot dipping) and > 100 ppm overall (Cherrie *et al.* 2001) Approx. 50% cases > 10 years' exposure Estimated exposure group[a] for workers with daily narcotic symptoms: very high.	Jobs using TCE (CAREX), exposure to solvent (JEM) Self-assessed: exposure + narcotic symptoms, duration (yr) and time since first and last exposure Range: not known, but may be shallow due to exposure from open conditions. Lagging 5-9, 10-19, 20 yr
Vamvakas *et al.* 1998 Hospital-based, Germany 1987–2002 *Adequate* *Limited number of subjects but exposed to high levels of TCE*	Small study: 58 RCC cases/84 controls Exposure prevalence: 33% (N = 19) cases; 6% (N = 5) controls	Very high exposure and long exposures Estimated to be 400 to 600 ppm during peak (hot dipping) and > 100 ppm overall (Cherrie *et al.* 2001) Mean duration of exposure among cases was 16 years and 7 years among controls Estimated exposure group[a] for highest rank exposure category: very high.	Ever/never and exposure category (ranked, integration of exposure time and symptoms) Range: not known, but may be shallow due to exposure from open conditions Lagging: no analysis
Other studies			
Christensen *et al.* 2013 Hospital and population-based, Canada 1975–1985 *Limited* *Few exposed cases and controls with substantial exposure*	Moderate size: 177 RCC cases/ 1999 cancer controls, 533 population controls Small size: 48 liver cases, 1834 liver cancer controls and 533 population controls Exposure prevalence: < 3% (N = 15 population controls; 63 cancer cases, and 5 RCC cases, 1 liver cancer) for any exposure	Levels and duration not reported. Occupations considered to have the highest exposure were mechanics and repairmen, metal machining occupations, electrical and electronics and metal shaping and formulation. Estimated exposure group for individuals with substantial exposure: assumed low (unclear because category includes	Any and substantial (integration of probability, frequency, concentration and duration) Range: not applicable Lagging: no analysis

Study Summary	Study size/Exposure prevalence	Reported or estimated exposure levels or duration	Exposure response analyses: Dose metrics /range lagging
	and controls and < 2 (N = 9 population controls, N = 2 RCC, 1 liver cancer) for substantial exposure	confidence of exposure).	
Pesch *et al.* 2000a Population-based, 5 German regions 1991–1995 *Limited* *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 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. Includes the Arnsberg and other regions; NAS (2006) estimated that most subjects had minimal contact with TCE averaging concentration of 10 ppm or less. Estimated exposure group for individuals with substantial exposure: assumed low (unclear because category includes probability of exposure).	Exposure index (ranked; integration of probability, duration and intensity) for two JEM and JTEM; Reported separately for men and women Range: Not applicable Lagging: no analysis
Dosemeci *et al.* 1999 Population-based, Minnesota, (USA) 1988–1999 *Limited to adequate* *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 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. Range: not applicable Lagging: no analysis

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	Misclassification of disease
NHL			
Christensen *et al.* 2013 Hospital and population-based, Canada 215 cases NHL, 533 controls	*Unlikely* Cases and cancer controls selected from same hospital and controls randomly from same underlying population using similar inclusion criteria 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 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* Histologically confirmed but older classification (ICD-9)
Cocco *et al.* 2013 and studies included in the analysis: ENGELA (Orsi *et al.* 2010) MIS (Miligi *et al.* 2006) EPILYMPH (Cocco *et al.* 2010) NCI-SEER (Purdue *et al.* 2011a) 3,788 cases NHL+ subtypes (DLBCL, FL, CLL), 4279 controls MM evaluated in Cocco *et al.* 2010	*Unlikely* 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. Population controls: EPILYMPH, NCI-SEER, MIS Hospital controls: EPILYMPH and ENGELA 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. NCI-SEER analysis also assessed average exposure, average weekly, and average exposure intensity for each subject. 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* Histologically confirmed; a subset re-reviewed in some studies; Classification harmonized using the WHO InterLymph consortium classification
Deng *et al.* 2013, Wang *et al.* 2009a	*Unlikely* Cases and matched controls selected	*Limited to adequate*: Occupational data on job titles and companies, genetic JEM based on	*Unlikely* Cases reviewed by pathologists;

Study and number of TCE-exposed cases/controls	Selection/participation bias	Quality of TCE exposure assessment and exposure misclassification	Misclassification of disease
Population-based Connecticut (USA) 601 NHL+subtypes cases, 7171 controls	from the same underlying population using similar inclusion criteria; Cases selected from cancer registry. 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. 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 Population-based (pooled study) Sweden 199 cases NHL, 479 controls	*Unlikely* Cases and matched controls selected from the same underlying population using similar inclusion criteria. Controls drawn for other studies and unclear which years controls were recruited. 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. 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 also likely.	*Possible* 2nd study histologically confirmed but not 1st study (not histologically confirmed); ICD coding NR
Nordstrom *et al.* 1998 Population-based Sweden 121 cases HCL, 484 controls	*Unlikely* Cases and matched controls selected from the same underlying population using similar inclusion criteria; Cancer selected from cancer registry. 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 self-report/occupation, qualitative; Minimal requirements for ever exposure based on very low exposure. Exposure misclassification is a concern and likely to be substantial.	*Possible* Subset of cases re-reviewed: NCI classification
Hardell *et al.* 1994 Population-based Sweden 105 cases NHL, 355 controls	*Unlikely* Cases and matched controls selected from the same underlying population using similar inclusion criteria; Cases selected from hospital dept. Participation rates: unknown	*Limited:* Complete occupational history (primarily job titles, not tasks or working conditions) and self-reported exposure; Exposure assigned based on self-report/occupation, qualitative; Minimal requirements for ever exposure based on very low exposure. Exposure misclassification is a concern and likely to be substantial.	*Possible* Cases histologically confirmed by subtype, stage, and site but older Rappaport classification.
Multiple Myeloma			

Study and number of TCE-exposed cases/controls	Selection/participation bias	Quality of TCE exposure assessment and exposure misclassification	Misclassification of disease
Gold *et al.* 2011 Seattle, WA and Detroit, MI (USA) SEER registry 181 cases MM, 481 controls	*Unlikely* Cases and matched controls selected from the same underlying population using similar inclusion criteria; Cases selected from cancer registry. 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.* 2011a for NH.). 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* Most SEER registry cases histologically confirmed; ICD – O-2 or 3)
Costantini *et al.* 2008 Population-based, Italy (MIS) 263 cases MM, 1100 controls; cases CLL NR; (total LH cases 2,737, 1799 controls)	*Unlikely* Cases and matched controls selected from the same underlying population using similar inclusion criteria . 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. 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* 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 Summary (study sensitivity)	Study size/exposure prevalence	Reported or estimated exposure levels or duration	Exposure response analyses: dose metrics/range Lagging
NHL			
Christensen *et al.* 2013 Hospital and population-based, Canada *Limited* *Small numbers of exposed cases and controls*	Moderate size: 215 NHL cases/23,141 cancer controls, 533 population controls 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. 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 Range: NA Lagging: no analysis
Cocco *et al.* 2013 and studies included in the pooled analysis: ENGELA (Orsi *et al.* 2010) MIS (Miligi *et al.* 2006 EPILYMPH (Cocco *et al.* 2010) NCI-SEER (Purdue *et al.* 2011a) *Adequate* *Adequate number of cases and controls all NHL but not all NHL subtypes; Estimated levels suggest levels relatively high for the highest exposed workers,.*	Very large study: 3788 cases/4279 controls Exposure prevalence in total population: 9% (N = 711) ever exposed, 1% (N = 88) definite exposed 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 Estimated levels NCI-SEER: levels not reported; levels estimated for analysis Highest cumulative exposure category: > 234,000 ppm-hr (prevalence: 0.7% controls, 2.5% cases) Highest average intensity exposure category: > 99 ppm (prevalence: 2.3% controls, 3.4% cases) MIS Study regions chosen because of large presence of manufacturing industries using solvents or they were agricultural areas.	Probability, intensity (ppm), frequency (% work time), duration (yrs) among all subjects and high probability subjects *Additional metrics in individual studies* Cumulative exposure (ranked): EPILYMPH, NCI-SEER (ppm-hr) Average weekly ppm-hr/week): NCI-SEER Sensitivity by latency, interviewing variable, & unemployment – NCI-SEER Range: Adequate range based on estimates of intensity, duration and frequency of exposure. Lagging: no analysis although NCI-SEER conducted 5 and 15 yr lagged analysis
Deng *et al.* 2013, Wang *et al.* 2009a Population-based Connecticut,	Large study: 601 NHL/ 717 controls Exposure prevalence: 11% controls	No information on reported or estimated level.	Exposure intensity (ranked), exposure probability Range: No information

Study Summary (study sensitivity)	Study size/exposure prevalence	Reported or estimated exposure levels or duration	Exposure response analyses: dose metrics/range Lagging
(USA) (Women) *Limited* *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.*	(N = 79) and 13% (N = 77) for 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		Lagging: no analysis
Gold *et al.* 2011 Seattle, WA and Detroit, MI (USA) SEER registry 181 cases MM, 481 controls *Adequate* *Adequate number of cases in control in subgroup analysis, including the highest exposure group*	Medium size study: 181 MM cases, 481 controls 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 (yrs.) and cumulative exposure (ppm-hrs) Range: adequate (estimated) range of exposures Lagging: 0, 10 yr
Costantini *et al.* 2008 Population-based, Italy *Limited statistical power* *Few exposed cases and controls*	Median size study: 263 cases MM, 1100 controls; cases CLL NR 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. Range: No information Lagging: no analysis
Persson and Fredrikson 1999 Population-based (pooled study) Sweden *Limited* *Relatively small number of exposed cases with possibly low levels of exposure*	Medium size study: 199 cases NHL, 479 controls 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. Minimum of 1 year exposure duration	Ever/never exposure only. Range: Not applicable

Study Summary (study sensitivity)	Study size/exposure prevalence	Reported or estimated exposure levels or duration	Exposure response analyses: dose metrics/range Lagging
Nordstrom *et al.* 1998 Population-based Sweden *Limited* *Relatively few exposed cases and controls with possibly low levels of exposure*	Small study: 121 cases NHL, 484 controls 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. Range: Not applicable Lagging: no analysis
Hardell *et al.* 1994 Population-based Sweden *Limited* *Few cases and controls with possibly low levels of exposure*	Small study: 105 cases and 355 controls 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 Range: Not applicable Lagging: no analysis

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 *et al*. 1995	X	X	X	X	X	X	X
Axelson *et al*. 1994	X	X	X	X	X	X	X
Bahr *et al*. 2011							X
Blair *et al*. 1998			X		X		
Boice *et al*. 1999	X		X	X	X	X	
Boice *et al*. 2006		X	X	X	X	X	X
Greenland *et al*. 1994	X	X		X	X	X	
Hansen *et al*. 2001	X	X	X	X	X	X	X
Lipworth *et al*. 2011		X					X
Morgan *et al*. 1998	X	X	X	X	X	X	X
Raaschou-Nielson *et al*. 2003	X	X	X	X	X	X	X
Radican *et al*. 2008	X	X	X	X		X	X
Ritz 1999		X			X		X
Zhao *et al*. 2005	X			X		X	
Case-control studies							
Asal *et al*. 1988		X					
Brüning *et al*. 2003	X	X	X				
Charbotel *et al*. 2006	X	X	X				
Cocco *et al*. 2010						X	X
Dosemeci *et al*. 1999	X	X	X				
Hardell *et al*. 1994						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]
Harrington *et al*. 1989		X					
Henschler *et al*. 1995		X	X				
Kato *et al*. 2005							X
Moore *et al*. 2010	X	X					
Miligi *et al*. 2006						X	X
Nordstrom *et al*. 1998						X	X
Persson and Frederickson 1999						X	X
Pesch *et al*. 2000a	X	X	X				
Purdue *et al*. 2011a						X	X
Siemiatycki 1991	X	X	X			X	X
Vamvakas *et al*. 1998		X	X				
Wang *et al*. 2009a						X	X

S-J = Scott and Jinot 2011 (see also EPA 2011a).
[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.* 2007: 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.

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 *et al* 2007b	48 wk				+	+						
Wang *et al.* 2012	12, 24, 36 wk				+	+						
Trichloroethylene; Mice (NOD/Born); Drinking water												
Ravel *et al* 2004	4, 8, 12 wk						-		-	-	-	-
Chloral hydrate; Mice (CD-1); Drinking water												
Kauffmann *et al* 1982	90 d						=					
Trichloroethylene; Rat (Sprague-Dawley); IP												
Halmes *et al* 1997	4 hr	+	+	+								
Chen *et al* 2006	5, 7 wk									-	=	
Trichloroethylene; Dog (cross-bred); Intratracheal intubation												
Hobara *et al* 1984	1 hr						-	-	=			
Hobara *et al* 1984	1, 4 hr						-	-	=			
Trichloroethylene; Dog (cross-bred); IV												
Hobara *et al* 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 and Doss 2007	Preconception to 4, 6, 8 wk old												=		
Cai *et al.* 2008	36, 48 wk										=				
Gilbert *et al.* 2009	10, 18, 26 wk									+					
Gilbert *et al.* 2011	8 wk									=	=				
Griffin *et al.* 2000a	4, 6, 8, 22 wk	+	+								+				
Griffin *et al.* 2000b	4, 32 wk										+				
Wang *et al.* 2007b	48wk										+		=		
Wang *et al.* 2012a	12, 24, 36 wk							+	+		+		+		
Trichloroacetic acid; Mice (MRL+/+); Drinking water															
Blossom *et al.* 2004	4 wk												=		
Trichloroacetaldehyde hydrate															
Blossom *et al.* 2004	4 wk												=		
Blossom *et al.* 2007	4, 40 wk												=	=	
Trichloroethylene; Mice (MRL+/+); IP															
Khan *et al.* 1995	6 wk	+	=								+	=	+		
Khan *et al.* 2001	6 wk								=						
Wang *et al.* 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 *et al.* 2008	4 wk	+						+	+		+				
Wang *et al.* 2013*	6 wk							+	+			+	+	+	
Dichloroacetyl anhydride; Mice (MRL+/+); IP															
Cai *et al.* 2006	6 wk	=		=			=				+				
Dichloroacetyl chloride; Mice (MRL+/+); IP															
Cai *et al.* 2006	6 wk	+		+			=				+				
Khan *et al.* 1995	6 wk	+	+								=	=	+		
Khan *et al.* 2001	2, 4, 6, 8 wk								+						
Trichloroethylene; Mice (MRL+/+); Inhalation															
Kaneko *et al.* 2000	4, 6, 8 wk	-													
Formyl-albumin adduct; Mice (MRL+/+); SC															
Cai *et al* 2007b	4 wk			+	+	+	+								
Dichloroacetyl-albumin adduct; Mice (MRL+/+); SC															
Cai *et al* 2007b	4 wk			+	+	+	+								
Trichloroethene oxide-albumin adduct; Mice (MRL+/+); SC															
Cai *et al* 2007b	4 wk			+	+	+	+								
Trichloroethylene; Mice (NZBWF1); Drinking water															
Keil *et al.* 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 *et al.* 2006	4, 40 wk												=	=	
Trichloroethylene; Mice ($B6C3F_1$); Drinking water															
Keil *et al* 2009	30 wk	+											+	+	
Peden-Adams *et al* 2006	Preconception to 3, 8, wk													=	
Trichloroethylene; Mice (CD-1); Drinking water															
Sander *et al* 1982	4, 6 mo														+/-
Chloral hydrate; Mice (CD-1); Drinking water															
Kauffmann *et al* 1982	90 d														=

* Included a group co-exposed to N-acetylcystine, an enhancer of the antioxidant activity of glutathione, which prevented the results

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

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 and Doss 2007	Preconception to 4, 6, 8 wk old				-		-		-		=			
Gilbert *et al.* 2011	8 wk				=		=		=					
Griffin *et al.* 2000a	4, 6, 8, 22 wk				=						=			
Griffin *et al.* 2000c*						+								
Peden-Adams *et al.* 2008	Preconception to 12 mo					=		=		=				
Trichloroacetic acid; Mice (MRL+/+); Drinking water														
Blossom *et al.* 2004	4 wk				=		=		=		=			
Trichloroacetaldehyde hydrate; Mice (MRL+/+); Drinking water														
Blossom *et al.* 2004	4 wk				=		=		=		=			
Blossom *et al.* 2007	4, 40 wk				-		=		=					
Trichloroethylene; Mice (MRL+/+); IP														
Wang *et al.* 2008	4 wk					+		=		=				
Dichloroacetyl anhydride; Mice (MRL+/+); IP														
Cai *et al.* 2006	6 wk	+												
Dichloroacetyl chloride; Mice (MRL+/+); IP														
Cai *et al.* 2006	6 wk	+												
Trichloroethylene; Mice (NZBWF1); Drinking water														
Keil *et al.* 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 *et al.* 2006	4, 40 wk				=		=							
Trichloroethylene; Mice ($B6C3F_1$); Drinking water														
Peden-Adams *et al.* 2006	Preconception to 3, 8 wk			=	+/-		=		-	=		-	=	
Keil *et al.* 2009	30 wk			=						=			=	
Wright *et al.* 1991	3 d													=
Trichloroethylene; Mice (CD-1); Drinking water														
Sander *et al.* 1982	4, 6 mo		+									+		
Chloral hydrate; Mice (CD-1); Drinking water														
Kauffmann *et al.* 1982	90 d			=						=		-		
Chloral hydrate; Mice (CD-1); Gavage														
Kauffmann *et al.* 1982	15 d								=					
Trichloroethylene; Rat (Sprague-Dawley); IP														
Wright *et al.* 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 *et al.* 2008	36, 48 wk						+			+	+			+
Gilbert *et al.* 2009	10, 18, 26 wk						+							
Griffin *et al.* 2000a	4, 6, 8, 22 wk	+												
Griffin *et al.* 2000b	4, 32 wk		+					+						=
Griffin *et al.* 2000c**	4, 32 wk		+											
Kondraganti *et al.* 2012	24, 36, 48 wk						+	+						
Trichloroethylene; Mice (MRL+/+); IP														
Wang *et al.* 2007a	6, 12 wk				+	+								
Wang *et al.* 2013*	6 wk				+	+						+	+	
Formyl-albumin adduct; Mice (MRL+/+); SC														
Cai *et al* 2007b	4 wk						+							
Dichloroacetyl-albumin adduct; Mice (MRL+/+); SC														
Cai *et al* 2007b	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 *et al* 2007b	4 wk						=							
Trichloroethylene; Mice (MRL+/+); Inhalation														
Kaneko *et al*. 2000	4, 6, 8 wk						+							
Trichloroethylene; Mice (NOD/Born); Drinking water														
Ravel *et al.* 2004	4,8, 12 wk						=							
Trichloroethylene; Mice (SV/129) [wt/PPAR-null/PPAR-tet-off]; Inhalation														
Ramdhan *et al.* 2010	7 d						+			+				
Trichloroethylene; Mice ($B6C3F_1$); IP														
Wright *et al.* 1991	3 d								-					
Trichloroethylene; Rat (Sprague-Dawley); IP														
Halmes *et al.* 1997	4 hr			+										
Wright *et al.* 1991	3 d								-					
Trichloroethylene; Guinea pig (FMMU); Dermal														
Tang *et al.* 2008	48 hr						=							
Trichloroethylene; Guinea pig (FMMU); Intradermal/Dermal														
Tang *et al.* 2008	23 d						=							
Trichloroethylene; Guinea pig (FMMU); Intradermal														
Tang *et al.* 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 *et al*. 2011	8 wk					=	=					
Gilbert *et al* 2012	12, 17 wk					=						
Wang *et al* 2012a	12, 24, 36 wk	+	+									
Trichloroacetic acid; Mice (MRL+/+); Drinking water												
Blossom *et al* 2004	4 wk					=	=	=	=			
Trichloroacetaldehyde hydrate; Mice (MRL+/+); Drinking water												
Blossom *et al* 2004	4 wk					=	=	=	=			
Trichloroethylene; Mice (MRL+/+); IP												
Wang *et al* 2008	4 wk	+	+	+	+							
Dichloroacetyl anhydride; Mice (MRL+/+); IP												
Cai *et al* 2006	6 wk			=	=							
Dichloroacetyl chloride; Mice (MRL+/+); IP												
Cai *et al* 2006	6 wk			+	+							
Trichloroethylene; Mice (C3H/HeJ); Drinking water												
Blossom *et al.* 2006	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 *et al* 1986	3 hr; 5 d									+		
Selgrade and Gilmour 2010	24, 72 hr; 20 d									+	+	
Trichloroethylene + Streptococcus zooepidermicus; Mice (CD-1); Inhalation + intratracheal instillation												
Selgrade and Gilmour 2010	3.5 hr											-
Trichloroethylene + kiebsiella pneumonia; Mice (CD-1); Inhalation												
Aranyi *et al* 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 12 hr	1.5* 1.4*	1.4* INS	Hassoun and Dey 2008
Dichloroacetic acid	7.7 77 154 410	4 wk	INS 1.8* 2.5* 3.7*	1.2* 2.5* 4.0* 4.3*	Hassoun and Cearfoss 2011, Hassoun *et al.* 2010b, Hassoun *et al.* 2010a
Dichloroacetic acid	7.7 77 154 410	13 wk	1.8* 2.4* 2.1* INS	1.4* 3.2* 4.3* 2.2*	Hassoun and Cearfoss 2011, Hassoun *et al.* 2010b, Hassoun *et al.* 2010a
Dichloroacetic acid	7.5 15 30	13 wk	1.8* 2.0* 2.2*	1.4* 1.9* 2.3*	Hassoun *et al.* 2013 Hassoun *et al.* 2014
Trichloroacetic acid	300 (single dose)	6 hr 12 hr	INS 1.5*	INS 1.2*	Hassoun and Dey 2008
Trichloroacetic acid	7.7 77 154 410	4 wk	INS 1.4* 1.9* 2.5*	INS INS 1.3* 2.8*	Hassoun and Cearfoss 2011, Hassoun *et al.* 2010b, Hassoun *et al.* 2010a
Trichloroacetic acid	7.7 77 154 410	13 wk	INS 2.0* INS INS	1.2* 1.8* 2.5* 2.8*	Hassoun and Cearfoss 2011, Hassoun *et al.* 2010b, Hassoun *et al.* 2010a
Trichloroacetic acid	12.5 25 50	13 wk	1.5* 1.6* 1.8*	1.3* 1.5* 1.7*	Hassoun *et al.* 2013 Hassoun *et al.* 2014
Mixtures	7.5/12.5[b] 15/25 30/50	13 wk	2.1* 2.7* 2.6*	1.7* 2.6* 3.2*	Hassoun *et al.* 2013 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 12 hr	1.3* 1.4*	2.6* 3.9*	Hassoun and Dey 2008
Dichloroacetic acid	7.7 77 154 410	4 wk	2.5* 5.0* 7.5* 14.0*	INS 3.5* 7.2* 7.2*	Hassoun and Cearfoss 2011, Hassoun *et al.* 2010b
Dichloroacetic acid	7.7 77 154 410	13 wk	3.5* 12.5* 15.0* 4.0*	1.6* 5.6* 5.6* 4.0*	Hassoun and Cearfoss 2011, Hassoun *et al.* 2010b
Dichloroacetic acid	7.5 15 30	13 wk	2.8* 4.0* 7.2*	1.6* 2.8* 4.0*	Hassoun *et al.* 2014
Trichloroacetic acid	300 (single dose)	6 hr 12 hr	INS 1.3*	INS 2.8*	Hassoun and Dey 2008
Trichloroacetic acid	7.7 77 154 410	4 wk	INS 2.0* 2.5* 11.0*	INS 1.8* 2.3* 4.3*	Hassoun and Cearfoss 2011, Hassoun *et al.* 2010b
Trichloroacetic acid	7.7 77 154 410	13 wk	1.5* 7.0* 8.5* 13.5*	INS 2.3* 3.3* 4.3*	Hassoun and Cearfoss 2011, Hassoun *et al.* 2010b
Trichloroacetic acid	12.5 25 50	13 wk	1.6* 2.6* 4.0*	INS 1.6* 2.0*	Hassoun *et al.* 2014
Mixture	7.5/12.5[b] 15/25 30/50	13 wk	3.2* 6.2* 13*	1.7* 3.6* 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 77 154 410	4 wk	INS 2.5* 4.1* 6.5*	5.0* 4.3* 12.3* 12.3*	INS 2.0* 3.0* 6.8*	Hassoun *et al.* 2010a
Dichloroacetic acid	7.7 77 154 410	13 wk	1.7* 3.7* 4.5* 5.2*	6.3* 10.8* 9.0* INS	2.4* 6.2* 5.2* INS	Hassoun *et al.* 2010a
Dichloroacetic acid	7.5 15 30	13 wk	– – –	5.3* 7.8* 9.3*	2.1* 2.7* 3.3*	Hassoun *et al.* 2013
Trichloroacetic acid	7.7 77 154 410	4 wk	INS 2.1* 4.0* 5.0*	36*[b] 52*[b] 66*[b] 18*[b]	INS 2.6* 4.3* 11.8*	Hassoun *et al.* 2010a
Trichloroacetic acid	7.7 77 154 410	13 wk	1.7* 2.6* 4.2* 5.2*	6*[b] 16*[b] 4*[b] INS	INS 3.0* INS INS	Hassoun *et al.* 2010a
Trichloroacetic acid	12.5 25 50	13 wk	– – –	5.7* 7.0* 9.5*	1.9* 2.2* 2.6*	Hassoun *et al.* 2013
Mixtures	7.5/12.5[b] 15/25 30/50	13 wk	– – –	9.5* 13.2* 12.5*	3.1* 4.1* 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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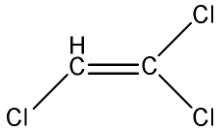
Trichloroethylene

CAS No. 79-01-6

Known to be a human carcinogen[1]

First listed in the *Ninth Report on Carcinogens* (2000)

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 epidemiological studies showing that it causes kidney cancer in humans, together with supporting evidence from toxicological, toxicokinetic, and mechanistic studies demonstrating the biological plausibility of its carcinogenicity in humans. Epidemiological studies also provide limited evidence for a causal association for 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. Trichloroethylene was first listed as *reasonably anticipated to be a human carcinogen* in the *Ninth Report on Carcinogens* in 2000, based on limited evidence of carcinogenicity from studies in humans, sufficient evidence of carcinogenicity from studies in experimental animals, and information from studies on mechanisms of carcinogenesis.

Cancer Studies in Humans

Kidney Cancer

Epidemiological studies have demonstrated a causal relationship between trichloroethylene exposure and kidney cancer based on consistent evidence of increased risk 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 (Raaschou-Nielsen *et al.* 2003, Hansen *et al.* 2013, Vlaanderen *et al.* 2013); several studies of workers in specific industries, including five studies in aerospace or aircraft manufacturing (Morgan *et al.* 1998, Zhao *et al.* 2005, Boice *et al.* 2006, Radican *et al.* 2008, Lipworth *et al.* 2011) 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

[1]NTP preliminary listing recommendation proposed for the RoC.

areas presumed to have elevated levels and prevalence of trichloroethylene exposure, in which exposure was assessed by experts with knowledge of the local industry (Vamvakas *et al.* 1998, Brüning *et al.* 2003, Charbotel *et al.* 2006, 2009, Moore *et al.* 2010), and three studies of more widespread populations with varying potential for exposure to trichloroethylene and overall lower average exposure (Dosemeci *et al.* 1999, Pesch *et al.* 2000, Christensen *et al.* 2013). 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). These studies were considered to have high utility to inform the cancer hazard evaluation 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 to have some utility to inform the cancer hazard evaluation.

The most convincing evidence for an association between trichloroethylene exposure and kidney cancer comes from the three most informative studies (Zhao *et al.* 2005, Charbotel *et al.* 2006, 2009, Moore *et al.* 2010), 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 (Morgan *et al.* 1998, Boice *et al.* 2006, Hansen *et al.* 2013, Bove *et al.* 2014, 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, and there was no evidence of publication bias in either meta-analysis. Increased risks were also found in separate meta-analyses of cohort and case-control studies.

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), the risk of kidney cancer increased with increasing level or duration of exposure as measured by several metrics (duration, intensity, and cumulative exposure). Further support for an exposure-response relationship is provided by one of the meta-analyses (Scott and Jinot 2011), which found a higher mRR for the highest exposure group across studies (mRR = 1.58, 95% CI = 1.28 to 1.96) than for all subjects ever exposed to trichloroethylene.

Although several studies (Greenland *et al.* 1994, Radican *et al.* 2008, Lipworth *et al.* 2011, Christensen *et al.* 2013, Vlaanderen *et al.* 2013), including some large studies, found little or no evidence for an association between kidney cancer and trichloroethylene exposure or for an exposure-response relationship, these studies were limited by non-differential exposure

misclassification or low sensitivity to detect an association because of either low exposure levels or small numbers of subjects with higher levels of exposure.

Biases or confounding by known or suspected occupational 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 between trichloroethylene and kidney cancer after controlling for smoking. Furthermore, the cohort studies found little evidence for an association between trichloroethylene exposure 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 (Zhao *et al.* 2005, Charbotel *et al.* 2006, 2009). Although co-exposures are not known for several other cohort and case-control studies, these studies included 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 provide limited evidence for a causal association between trichloroethylene exposure and NHL, based on positive associations in several studies and evidence for increased risk of NHL across studies combined in two meta-analyses. The evidence across studies is less consistent than for kidney cancer, and alternative explanations such as chance or confounding cannot reasonably be ruled out.

Studies reporting risk estimates specific for NHL (including its 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 (Morgan *et al.* 1998, Raaschou-Nielsen *et al.* 2003, Boice *et al.* 2006, Radican *et al.* 2008, Lipworth *et al.* 2011, Hansen *et al.* 2013, Vlaanderen *et al.* 2013, Bove *et al.* 2014, Silver *et al.* 2014) and an additional study of uranium processing workers (Bahr *et al.* 2011). (One study of aerospace manufacturing workers [Zhao *et al.* 2005], the study of cardboard manufacturing workers [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 (Wang *et al.* 2009, Deng *et al.* 2013), 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 study because of its high-quality exposure assessment, large size, and analyses of exposure-response relationships and NHL histological subtypes.

The strongest evidence for an association between trichloroethylene exposure and NHL comes from the InterLymph pooled analysis (*P* for Fisher's combined probability = 0.004) and the two meta-analyses (mRR = 1.23, 95% CI = 1.07–1.42, Scott and Jinot 2011; mRR = 1.32, 95% CI = 1.14–1.54, 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; however, this analysis showed low to moderate heterogeneity across studies and some evidence of publication bias. The meta-analysis by Karami *et al.* showed little evidence of publication bias or of heterogeneity across studies. The risk of NHL increased with increasing 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 trichloroethylene exposure and NHL also comes from increased risks of NHL found in several case-control studies (Hardell *et al.* 1994, Wang *et al.* 2009) and cohort studies (Morgan *et al.* 1998, Raaschou-Nielsen *et al.* 2003, Radican *et al.* 2008, Lipworth *et al.* 2011, Hansen *et al.* 2013). 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 elevated risks found in the meta-analyses. There was little evidence (Persson and Fredrikson 1999, Christensen *et al.* 2013, Bove *et al.* 2014) or no evidence (Bahr *et al.* 2011, Vlaanderen *et al.* 2013, Silver *et al.* 2014) of an association between trichloroethylene exposure and NHL in the other studies, most of which had limited exposure assessments that limited sensitivity to detect an effect for an uncommon cancer such as NHL. Only one exposed case was observed in the study of aerospace workers (Boice *et al.* 2006) and thus was not informative.

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 (Purdue *et al.* 2011, Cocco *et al.* 2013).

Liver Cancer

The available database for liver cancer included twelve cohort or nested case-control studies (Morgan *et al.* 1998, Ritz 1999, Raaschou-Nielsen *et al.* 2003, Boice *et al.* 2006, Radican *et al.* 2008, Bahr *et al.* 2011, Lipworth *et al.* 2011, Hansen *et al.* 2013, Vlaanderen *et al.* 2013, Bove *et al.* 2014, Greenland *et al.* 1994, Silver *et al.* 2014) and two meta-analyses (Alexander *et al.* 2007, Scott and Jinot 2011). The only available case-control study (Christensen *et al.* 2013) was not informative because there was only one trichloroethylene exposed case of liver cancer. 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, the findings are inconsistent across studies, and there was little evidence for exposure-response relationships in the individual studies or the meta-analyses. In addition, the role of chance or confounding by one or more common occupational co-exposures or lifestyle factors cannot 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 (NCI 1976, Maltoni *et al.* 1988, NTP 1990, IARC 1995), and 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).

Studies on Mechanisms of Carcinogenesis

The available evidence indicates that trichloroethylene causes genotoxicity, toxicity, and cancer via its 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 through 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 experimental 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). Metabolism of trichloroethylene is qualitatively similar in humans and experimental animals. *In vitro* studies in kidney and liver cells from humans and rodents have demonstrated 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 importance of the GSH-conjugation pathway in humans is supported by the finding of a significantly elevated 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).

The available mechanistic data support a mutagenic and cytotoxic mode of action mediated by GSH-conjugated metabolites (EPA 2011). These metabolites have been shown to be genotoxic or related effects 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.* A mechanism that may potentially contribute to trichloroethylene's carcinogenicity is cytotoxicity and associated regenerative proliferation (EPA 2011). Studies in humans also provide evidence that trichloroethylene causes nephrotoxicity (Brüning *et al.* 1999a,b, Bolt *et al.* 2004, 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 could cause lymphoma are largely unknown. Immune disorders, including autoimmunity and immunosuppression, are strongly linked to NHL (Hardell *et al.* 1998, Baecklund *et al.* 2014, Ponce *et al.* 2014). There is evidence that trichloroethylene causes immunomodulation in both humans and animals (EPA 2011),

suggesting a biologically plausible role for immunomodulation in induction of NHL by trichloroethylene. It has been proposed that lymphomas can develop from errors arising during the somatic hypermutation phase of B-cell activation, resulting 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 (Peden-Adams *et al.* 2006, 2008, Keil *et al.* 2009, Lan *et al.* 2010, Hosgood *et al.* 2012, Bassig *et al.* 2013). 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 in mice is unknown but likely is complex, involving key events in several pathways (EPA 2011). Studies in experimental animals provide evidence for several potential modes of action, including genotoxicity, oxidative stress, peroxisome proliferation, epigenetic events, and autoimmune hepatitis (EPA 2011, Wang *et al.* 2013). Oxidative metabolites are considered to be more important than GSH-pathway metabolites in liver carcinogenicity because trichloroethylene and its metabolites trichloroacetic acid, dichloroacetic acid, and chloral hydrate have similar hepatotoxic and hepatocarcinogenic effects. These oxidative metabolites are formed in humans, and some genotoxic effects have been reported 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 2014). 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 2014.

Use

Trichloroethylene is used as an intermediate in hydrofluorocarbon production (83.6%) and as a degreaser for metal parts (14.7%) (EPA 2014). The remaining 1.7% is attributed to "other

uses," which include use in clear protective spray coatings for use by arts and crafts hobbyists and as a modifier in polyvinyl chloride polymerization. Past use of trichloroethylene was primarily as a degreaser; however, that use in the United States declined beginning in the 1970s (Bakke *et al.* 2007). Industrial groups that may currently use trichloroethylene in vapor or cold degreasing operations include fabricated metal products, electrical and electronic equipment, transportation equipment, and miscellaneous manufacturing industries. Trichloroethylene has also been used as an industrial solvent in the rubber industry, and in paints, lacquers, varnishes, adhesives, and paint strippers, and in the production of agricultural chemicals such as fungicides and insecticides (IARC 1995, Bakke *et al.* 2007).

Trichloroethylene is listed as a major ingredient in several consumer products such as household aerosol products for arts and crafts uses and consumer degreasers intended for use in auto products, home maintenance, or commercial/institutional use (HPD 2014, EPA 2014). Other consumer products containing trichloroethylene that have been identified include typewriter correction fluids, paint removers and strippers, adhesives, spot removers, and rug-cleaning fluids (Gist and Burg 1995).

In the past, trichloroethylene was used as an extraction solvent for natural fats and oils, spices, hops, and caffeine (in coffee); as an anesthetic and analgesic in obstetrics and for minor surgical procedures; in cosmetics and drug products and as a dry cleaning agent. However, its use for dry cleaning essentially ceased by the 1950s and for the other uses by the 1970s (IARC 1995, Bakke *et al.* 2007).

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	225
U.S. imports[b]	2013	2.4
U.S. exports[b]	2013	25.5

Sources: [a]EPA 2013. [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 decreased steadily to less than 5% of that level for 2010 to 2013 (USITC 2014). Between 1989 and 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 (IPCS 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 population can be exposed to trichloroethylene in ambient air, drinking-water supplies, 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, and exposure in these areas of past use or disposal of trichloroethylene continue to be reported. However, recent measurements of trichloroethylene blood levels in the general population suggest an overall decrease in exposure. Several additional lines of evidence support this trend, including recent decreases in total imports of trichloroethylene, decreased estimates of the numbers of exposed workers, decreased use of trichloroethylene for solvent degreasing in large commercial and industrial settings, and declining environmental releases of trichloroethylene.

The U.S. Environmental Protection Agency's (EPA's) Office of Chemical Safety and Pollution Prevention (EPA 2014) estimated that approximately 30,000 workers and occupational bystanders would be exposed to trichloroethylene at small commercial degreasing operations and approximately 300,000 workers and occupational bystanders would be exposed at dry cleaning operations using trichloroethylene as a spotting agent. Production of hydrofluorocarbon refrigerant and solvent degreasing in large commercial and industrial settings were considered by EPA to have low potential for human exposure to trichloroethylene because of the use of closed-loop process systems and regulatory monitoring and control (EPA 2014). Higher numbers of exposed workers (401,373 workers at 23,225 facilities) were estimated in the National Occupational Exposure Survey conducted from 1981 to 1983 (NIOSH 1990).

Although exposure in occupational settings such as solvent degreasing in large commercial/industrial facilities has decreased over time due to regulatory monitoring and control, 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 (OSHA 2013). From 2000 to 2010, 92 samples had concentrations above the OSHA permissible exposure limit (PEL) of 100 ppm, including 2 samples with concentrations above the National Institute for Occupational Safety and Health "immediately dangerous to life or health" level of 1,000 ppm.

According to 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. Trichloroethylene is a common groundwater and drinking-water contaminant (Gist and Burg 1995, IARC 1995, ATSDR 1997, 2013, Heneghan 2000, 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 was reported 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).

Exposure of the general population to trichloroethylene is primarily by inhalation of ambient air and ingestion of contaminated drinking water (ATSDR 1997, 2013). The decrease in releases of trichloroethylene to the environment may help to explain the decreased blood levels of trichloroethylene detected in the general population in recent years. 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) (Wu and Schaum 2000). 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 (CDC 2009a,b, 2011).

Several studies of air levels since the 1980s indicate that trichloroethylene levels are generally lower for recent samples, consistent with the overall decrease in releases to the air and in blood levels in the general population. According to monitoring data from EPA's Air Quality System, trichloroethylene levels in ambient air remained fairly constant from 1999 to 2006, with a mean level of approximately 0.3 $\mu g/m^3$ (0.000056 ppm); however, the data were not from a statistically based survey and may not be nationally representative (EPA 2011). As part of the Minnesota Children's Pesticide Exposure Study, personal, indoor-air, and outdoor-air trichloroethylene concentrations were measured from May to September 1997 in 284 households with children. The median values for indoor, outdoor, and personal sampling were all between 0.5 and 1 $\mu g/m^3$ (0.00009 to 0.0002 ppm) (Adgate *et al.* 2004). Trichloroethylene concentrations in ambient air were also 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).

Vapor intrusion (migration of volatile chemicals from the subsurface into overlying buildings) likely makes an important contribution to indoor air levels where offices or residences are located near soil or groundwater with high contamination levels (EPA 2011). Environmental occurrences of trichloroethylene have been reported in locations near sites of past use or disposal (e.g., National Priorities List Superfund sites). Elevated levels of trichloroethylene in indoor air at Superfund sites were reported for office buildings in Mountain View, California (Rust and Drange 2013), and homes in Asheville, North Carolina (Morrison 2014). Trichloroethylene concentrations were as high as 110 $\mu g/m^3$ in office buildings at the Mountain View site when the heating, ventilation, and air conditioning system was not operating (Welt and Bice 2013) and 14 $\mu g/m^3$ in the basement of a house at the Asheville site.

Trichloroethylene volatilizes readily from contaminated tap water, and inhalation exposure to 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), and another study (Weisel and Jo 1996) determined that approximately equal amounts of trichloroethylene entered the body via inhalation, dermal absorption, and ingestion during typical daily activities where contaminated tap water was used for drinking and bathing (including showering). However, a modeling study of trichloroethylene exposure of workers showering with trichloroethylene-contaminated water at a metal degreasing facility (Franco *et al.* 2007) estimated that dermal exposure contributed more than inhalation exposure to carcinogenic risk. Based on a trichloroethylene concentration of 3.0 μg/L in drinking water (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 is a major ingredient in several consumer products, including household aerosol products. For example, it constitutes 80% to 100% of three products for arts and crafts uses (e.g., clear plastic protective coating sprays) and three other products intended for use as cleaners or degreasers in automobile or home maintenance (EPA 2014, HPD 2014). However, in its risk assessment, EPA (2014) was not able to estimate the numbers of consumers or bystanders exposed to trichloroethylene from arts and crafts spray products or degreasers.

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, or caffeine (from coffee) since the FDA imposed limitations on these uses in 1977, foods can still be contaminated with trichloroethylene through the use of contaminated water in food processing or of 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 = 5×10^{-2} per mg/kg b.w. per day.

IRIS inhalation unit risk = 2×10^{-2} per ppm [4×10^{-6} per $\mu g/m^3$].

Regional Screening Levels (formerly 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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