Chemical Substances and Biological Agents

Studies and Research Projects

REPORT **R-653**

A review of selected literature (1995-2009) on the carcinogenicity of trichloroethylene (TCE)

Pete Watts
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This study was financed by the IRSST. It focuses on the exposure consequences of trichloroethylene in workplace. The conclusions and recommendations are those of the authors.

SYNOPSIS

Introduction

In 1995, a Working Group of the International Agency for Research in Cancer concluded that trichloroethylene (trichloroethene; TCE; CAS Registry Number 79-01-6) can cause cancer in laboratory rodents, and is probably carcinogenic to humans (IARC, 1995). To establish whether these conclusions have been significantly modified by the more recent scientific literature, an updating review was produced for the Institut de Recherche Robert Sauvé en Santé et en Sécurité du Travail (IRSST). This review focused on the most recent 10-15 years of the literature, covering the period post-dating the 1995 IARC evaluation.

This review was carried out jointly by scientists at the University of Utrecht in the Netherlands and at Toxicology Advice & Consulting Ltd[1] in the UK. The major focus was on the most informative epidemiology studies published since the 1995 IARC review. These were summarised (see tables) and the most informative studies were discussed in the main text in more detail. The single relevant new laboratory animal cancer study was also summarised. A brief overview of the TCE cancer data evaluated by IARC (in humans and laboratory animals) was also included. Available mechanistic data relatring to the probable modes-of-action underlying the development of tumours in TCE-exposed rodents were also summarised briefly, to assist in determining whether rodent tumours might be predictive of similar effects in TCE-exposed humans. The report also assessed, to the limited extent possible, whether there was any evidence that cancer target tissues depended upon the TCE exposure route.

IARC (1995) conclusions

The 1995 IARC review had concluded that TCE caused cancer in laboratory rodents. In two adequate chronic oral studies in mice, TCE induced benign and malignant liver tumours. Most of the seven oral TCE cancer studies in rats were inconclusive (because treatment time was too short or survival was reduced), but two studies found increases in uncommon kidney tumours in males. Increases in lung tumours were seen in three of the four lifetime inhalation studies in mice, and liver tumours or lymphomas were increased in individual studies. In one of the three rat lifetime inhalation studies, the males showed an increase in kidney tumours. No evidence of carcinogenic activity was seen in hamsters exposed to TCE by the inhalation route for lifetime.

In 1995, IARC evaluated a number of cohort and case-control studies exploring TCE's potential ability to induce cancer in occupationally-exposed workers. The most informative of the cohort studies were consistent in giving limited evidence of an increased risk of cancer of the liver and biliary tract and a modestly elevated risk of non-Hodgkin's lymphoma. Case-control studies, which by nature are generally less informative than cohort studies, gave inconsistent results. Two residential studies carried out in areas where TCE had contaminated the groundwater suggested a marginal increase in non-Hodgkin's lymphoma in the TCE-exposed population. Overall, IARC concluded in 1995 that there was limited evidence for TCE's carcinogenicity in humans, and classified it in Group 2A as a "Probable human carcinogen".

[1] Now bibra – toxicology advice & consulting.

Recent (post-1995) literature findings

The only identified relevant post-1995 cancer study in laboratory animals involved drinking-water exposure of mice to TCE as a major component of a mixture of chlorinated alkanes/alkenes, and this gave limited evidence of an increase in liver tumours, which is consistent with other available mouse studies on TCE.

The more recent epidemiological evidence summarised in this review adds very little in the way of strong additional evidence. One newer, well-designed study that used the urinary concentrations of a TCE metabolite (trichloroacetic acid; TCA) to indicate the degree of TCE exposure (i.e. as a biomarker) found a positive association between this estimate of TCE exposure and non-Hodgkin's lymphoma and thus adds some, albeit limited, evidence. Overall, the picture has changed little since the IARC evaluation, especially as some of the newer studies that found no evidence of an effect were not very informative. Findings from cohort studies with less accurate assessment of TCE exposure have been more variable in terms of associations between exposure and cancer. TCE exposure has been assessed even less accurately in case-control studies, with very few exceptions, and was often simply estimated from exposures to solvents in general. These studies typically reported higher cancer risks for the tumour sites that were similar to those observed in the cohort studies.

Other Expert Groups have assessed the TCE cancer literature since the IARC review. A Risk Assessment Report produced for the European Union regulators concluded (in 2004) that the major cancer concerns for TCE-exposed humans centred on non-Hodgkin's lymphoma and the kidney. A 2009 draft report from the US Environmental Protection Agency described the evidence for TCE's ability to induce cancer in humans as convincing for the kidney, less convincing but still compelling for non-Hodgkin's lymphoma, and more limited for the liver and biliary tract.

Conclusions

TCE has induced cancer in laboratory rodents. The evidence is strongest for liver tumours in mice (exposed by the oral or inhalation routes), lung tumours in mice (exposed by inhalation) and kidney tumours in rats (exposed orally or by inhalation).

In agreement with the earlier Expert Group assessments, it is concluded that the epidemiological investigations with more reliable exposure assessment components provide some indications that TCE is potentially carcinogenic to humans. Excess risks are generally below a factor of 2 (i.e. the cancer risk among exposed workers is less than twice that of non-exposed) for cancer at any of the tissue sites that have been considered, and these excess risks may be mainly associated with the higher exposures that the workers would probably have experienced in the more distant past.

In respect of cancer target tissue and possible TCE exposure route specificity, useful human data are restricted to the inhalation route and thus provide no real opportunity to assess any exposure-route specificities in target tissue for TCE and cancer. The available information was generally too limited to allow a detailed assessment of the minimum duration of exposure or latency period associated with an increased cancer risk. Where information was available, the inclusion of a 20-year latency period in the analysis resulted in an increase in cancer risk.

Lifetime bioassays are available in rats and mice exposed both orally and by inhalation, providing an opportunity to study the possible existence of relationships between cancer target tissue and these two exposure routes. Dermal exposure data are essentially lacking. Rats showed no evidence of route specificity, developing low incidences of kidney tumours following either oral or inhalation exposure to TCE. Mice were similar in that they developed liver tumours following exposure by either of these routes. However, lung tumours were seen in mice only following inhalation exposure, and this is believed to be due to an accumulation of carcinogenic chloral hydrate in the Clara cells of the lungs, which are directly exposed during inhalation of TCE.

Overall, the current thinking within Expert Groups is that the mouse lung and liver tumours are unlikely to be relevant to humans, based on the weight-of-evidence regarding mechanism and mode-of-action. However, there is a greater uncertainty about the possible relevance of the kidney tumours in rats, because the mechanisms have not been fully elucidated and, where data are available, it is not obvious that humans would respond differently.

In conclusion, the more robust epidemiological investigations of workers exposed to TCE in the occupational setting have provided some evidence that TCE is potentially carcinogenic to humans. Excess cancer risks are not large and may be mainly associated with the higher exposures that the workers would probably have experienced in the more distant past. An association between occupational TCE exposure and cancer in humans was most consistently found for kidney cancer and non-Hodgkin’s lymphoma, with more limited evidence for liver cancer and biliairy tract.

TABLE OF CONTENTS

1. INTRODUCTION

The Institut de Recherche Robert Sauvé en Santé et en Sécurité du Travail (IRSST) commissioned scientists from the University of Utrecht (in the Netherlands) and Toxicology Advice & Consulting Ltd (in the UK) to produce a review of selected literature on the carcinogenicity of trichloroethylene (trichloroethene; TCE; CAS Registry Number 79-01-6).

Specifically, the remit was to review the most recent 10-15 years of the literature, a period that in effect covers the time since the most recent expert evaluation of TCE's cancer potential by a Working Group of the International Agency for Research on Cancer (IARC, 1995). The present review focused on informative epidemiology studies published since the IARC review. In addition, searches were carried out to determine whether any post-IARC TCE cancer studies have been carried out in laboratory animals.

A brief overview of the knowledge database of TCE's cancer potential (both in humans and laboratory animals) at the time of the IARC review was also included. Available data on the likely mechanisms that led to tumours in TCE-exposed rodents were summarised briefly, to assist in determining whether rodent tumours might be predictive of similar effects in exposed humans.

2. RECAP OF ISSUE, EXISTING KNOWLEDGE AND RESEARCH OBJECTIVES

Trichloroethylene (TCE) is known to cause cancer in laboratory rodents, based on studies published before 1995. On chronic administration by the oral route, it increased the incidence of liver tumours in mice and kidney tumours in rats. Following inhalation for lifetime, mice experienced increases in lung and liver tumours (and possibly lymphomas), while one of the rat studies found increases in kidney and testicular tumours. Limited studies involving dermal application of TCE or its proposed metabolite TCE-oxide did not increase local tumour incidence (IARC, 1995). Overall, the evidence is strongest for liver tumours in mice (exposed by the oral or inhalation routes), lung tumours in mice (exposed by inhalation but not after ingestion) and kidney tumours in rats (exposed orally or by inhalation).

A number of cohort and case-control studies exploring TCE's potential ability to induce cancer in humans were also published before 1995. The most informative cohort studies consistently gave limited evidence of an increased (approximately two-fold) risk of cancer of the liver and biliary tract, and of a modest elevation (about 1.5-fold) in risk of non-Hodgkin's lymphoma. Case-control studies gave inconsistent results. Two community studies carried out in areas where TCE had contaminated the groundwater suggested a marginal increase in non-Hodgkin's lymphoma (IARC, 1995).

In contrast to laboratory animal studies, where adequate numbers of animals of each sex can be examined in detail after deliberate exposure, to one specific substance, at maximum-tolerated and well-defined levels for lifetime, the nature of epidemiological studies means that it is more

difficult to confidently assign any given exposure to a specific chemical agent as the cause of any apparent increase in cancer risk within an exposed population. Such populations are genetically heterogeneous, are generally exposed to relatively low levels, often for varying times, with exposures that possibly start and end at different ages, and are likely to have been exposed to many chemicals. The International Agency for Research on Cancer last assessed the TCE cancer epidemiology together with the laboratory animal bioassays in February 1995, and concluded that there was "limited" evidence for carcinogenicity in humans and "sufficient" evidence in laboratory animals, leading to an overall placement of TCE in Group 2A ("probably carcinogenic to humans") (IARC, 1995).

In the nearly 15 years since it was last evaluated by IARC, additional investigations relevant to the potential of TCE to cause cancer in humans have been published. Consequently, in order to understand the current position on this issue, a summary of the more recent literature was required. More recent Expert Group assessments of TCE and cancer are now available. The outcome of an assessment by EU Specialised Experts and the EC's Working Group on the Classification and Labelling of Dangerous Substances was TCE's classification as a Category 2 carcinogen i.e. one that "should be regarded as carcinogenic to humans; there is sufficient evidence to provide a strong presumption that human exposure to the substance may result in the development of cancer" (ECB, 2004). In 2009, the US Environmental Protection Agency published a draft Toxicological Review on TCE for public comment (under its IRIS program), describing the evidence for TCE's ability to induce cancer in humans as convincing for the kidney, less convincing but still compelling for non-Hodgkin's lymphoma, and more limited for the liver and biliary tract.

Carcinogens can induce cancer at one or more tumour sites, and the sites might vary depending upon exposure routes, especially if the carcinogen induces tumours at the site of first contact. The available data were assessed to determine whether they support any conclusions assigning specific exposure routes to particular target sites for TCE-induced cancer.

In this report, the key tasks that were carried out can be summarised as follows:

1. Identification and review of recent (10-15 years) epidemiological studies regarding the potential relationship between TCE exposure and generation of tumours as a function of route of exposure (ingestion, inhalation, dermal).

2. Identification and review of recent (10-15 years) laboratory animal studies, following good laboratory practices (GLP), investigating the potential relationship between TCE exposure and generation of tumours as a function of route of exposure (ingestion, inhalation, dermal).

3. Differentiation between tumours (malignant or non-malignant).

4. As far as possible, evaluation of the strength of the association if an increased incidence of cancer is identified.

5. As far as possible, evaluation of latency period anticipated for each specific cancer by route of exposure if applicable.

To assist in interpretation of the more recent (1995-present) literature in the context of the earlier knowledge, it was also necessary to summarise the scientific understanding of TCE's cancer potential as of 1995. Key existing expert information sources were accessed to produce this summary (ECB, 2004; IARC, 1995; USEPA, 2009); see Section 3.

3. METHODS

3.1 Recent (1995-2009) cancer literature

The primary remit of this project was to identify, summarise and assess the most recent 10-15 years of published knowledge on TCE's ability to induce cancer in humans and other mammals.

The two primary initial sources of relevant publications were the Toxline and TRACE databases. The TOXLINE database[2] is the National Library of Medicine's bibliographic database for toxicology and provides bibliographic information covering the biochemical, pharmacological, physiological, and toxicological effects of drugs and other chemicals. It contains over 3 million bibliographic citations, most with abstracts and/or indexing terms and CAS Registry Numbers. The TRACE database[3] is used to interrogate the bibra in-house toxicity databank. This databank has been constructed over the past 45 years, by bibra toxicologists who scan a large number of primary and secondary toxicity data sources on a daily basis. Selected papers are indexed and added to the databank. TRACE (see Appendix) includes information from peer-reviewed toxicology and nutrition journals as well as secondary sources and websites. In addition to primary literature on the health effects of chemicals, TRACE covers official publications and evaluations issued by authoritative groups. The TRACE database has been independently evaluated as the most effective tool available for identifying documents critical to the toxicological risk assessor. It demonstrates greater selectivity and targeting than any other comparable online database (Anderson et al. 2000; Robinson et al. 2000). It has also been listed as a valuable data source in the official European Chemicals Agency (ECHA) Guidance on the identification of toxicity data for REACH, the European legislation on the Registration, Evaluation, Authorisation and Restriction of Chemicals (ECHA, 2008).

TOXLINE and TRACE were each searched using the CAS Registry Number (RN) for TCE. In TOXLINE, standard indexing terms assigned to papers on carcinogenicity were included in the search. In TRACE, each selected paper is indexed by chemical name, CAS RN, and other descriptors relating to tested species, exposure route, exposure duration and toxicological endpoint. Thus Toxline and TRACE were used to identify 1995-2009 papers relating to TCE and cancer. This included primary literature, expert reviews and Expert Group reports.

This process initially identified about 70 potentially relevant papers, and each was evaluated for inclusion in this report. In addition, the reference lists of this initial set of papers were assessed for any further studies of potential relevance. This identified about a dozen additional publications. These were obtained and evaluated for inclusion in this report. Finally, recent

[2] See http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE for further details.

[3] See http://www.bibra-information.co.uk/trace.html for further details.

Expert Group reports and other reviews were consulted to ensure that all key studies had been evaluated and included.

The selected studies were summarised in tabulated form (see Tables 1-3). The templates and guidelines for tables that IARC currently gives to the authors of the first drafts of IARC monographs were adopted as a suitable model for tabulated study summaries.

3.2 Earlier (pre-1995) cancer literature

To assist in interpretation of the more recent literature, it was necessary to briefly recap what was the scientific understanding of TCE's cancer potential in 1995. For this purpose, the major information sources were the IARC monograph (IARC, 1995) and the Risk Assessment Report (RAR) published by the European Commission (ECB, 2004).

A brief overview of the TCE cancer literature up to 1994 was generated. This section of the literature was not analysed in detail again, having been expertly evaluated by IARC (IARC, 1995).

3.3 Rodent tumours – mode-of-action and relevance to humans

While there is clear evidence that TCE can cause tumours in laboratory rodents, the focus of interest in this report is on TCE's potential ability to induce tumours in humans. In order to determine whether the laboratory animal tumour data make a useful contribution to the risk characterisation and risk assessment of TCE exposure in humans, it is helpful to understand the modes-of-action by which the laboratory animal tumours arose. To assist in assessing the relevance of the rodent tumours to man, an overview of the understanding of the mechanisms underlying the rodent tumours is provided. This relied heavily upon Expert Group pronouncements (e.g. ECB, 2004; HC, 2005; IARC, 1995; NRC, 2006; WHO, 2008) and, because this is not a focal issue of the present report, has not been updated further.

4. RESULTS

4.1 Cancer epidemiology overview (up to 1995)

The literature on the epidemiology of TCE and cancer had been reviewed in 1995 by the World Health Organization's International Agency for Research on Cancer (IARC, 1995). That IARC review considered three cohort studies to be particularly relevant to the TCE assessment. Two of these studies were carried out in Sweden (Axelson et al. 1994) and Finland (Anttila et al. 1995) and involved people who had been monitored for TCE exposure by measuring urinary concentrations of the metabolite trichloroacetic acid (TCA). Monitoring suggested that exposure levels were generally low. The third study was of workers exposed to TCE (some were also exposed to other solvents) during maintenance of US military equipment (Spirtas et al. 1991). A fourth cohort study, of US aircraft manufacturing workers, was considered less relevant as only

about one-third of the workers were exposed to TCE and exposure could not be categorized (Garabrant et al. 1988). These four studies are summarized below, and in Table 1.

In the first of the key studies, the analysis was based on 1670 workers (1421 men and 249 women) from 115 companies that had purchased TCE from a production plant in Sweden, and taken advantage of the producer's free surveillance of their exposed workers (which involved analysis of TCA in the urine). The workers were followed up for mortality from 1955 through 1986 and for cancer incidence from 1958 through 1987. Swedish national rates were used for the calculation of expected numbers of cancers. Exposure was assessed as the mean concentration of TCA in all urinary samples available for a given worker. For men, the categories 0-49, 50-99 and > 100 mg/L accounted for 78, 14 and 8% of the person-years, respectively. There were 253 deaths in total, giving an overall standardized mortality ratio (SMR) of 1.0 (95% confidence interval (CI): 0.89-1.1), and 129 incident cancer cases occurred, giving an overall standardized incidence ratio (SIR) of 1.0 (95% CI: 0.84-1.2). Of the incident cancer cases in men, 77 occurred in the lowest exposure category (SIR = 0.92), 18 in the medium category (SIR = 0.93) and 12 (SIR = 1.4) in the highest exposure category. Among men, a significant excess risk was found only for skin cancer (SIR = 2.4; 95% CI: 1.0-4.7; 8 observed), and there were elevated SIRs for non-Hodgkin's lymphoma (SIR = 1.6; 95% CI: 0.51-3.6; 5 observed) and liver and biliary tract cancer (SIR = 1.4; 95% CI: 0.38-3.6; 4 observed) (Axelson et al. 1978, 1984, 1994).

The second key cohort study evaluated 3974 persons in Finland who were biologically monitored for occupational exposure to three halogenated hydrocarbons (3089 for TCE, 849 for tetrachloroethylene and 271 for 1,1,1-trichloroethane) during 1965-1983. Based on nearly 11,000 measurements, the overall median urinary concentrations of TCA were 10.3 and 7.8 mg/L in women and men, respectively. The cohort was followed up for incident cancer cases through 1992, and Finnish national cancer rates were used as the comparison basis. In the 3089 workers monitored for TCE exposure, there were 208 cancer cases (SIR = 1.1; 95% CI: 0.92-1.2). A significant excess risk was seen for cervical cancer (SIR = 2.4; 95% CI: 1.1-4.8; 8 observed), and the risk was further increased for women with a mean urinary TCA level ≥ 16.3 mg/L (SIR = 4.4; 95% CI: 1.4-10; 5 observed); there was no further increase in risk with increasing latency since the time of first measurement. The SIR for liver cancer among people with high exposure was 2.7 (95% CI: 0.33-9.9; 2 observed), and became statistically significant when a 20-year latency period since first measurement was incorporated (SIR = 6.1; 95% CI: 1.3-18; 3 observed). For cancers of the lymphohaematopoietic tissues, the SIR was increased among people with high exposure (SIR = 2.1; 95% CI: 0.95-4.0; 9 observed) and further increased with the 20-year latency addition (SIR 3.0; 95% CI: 1.2-6.1; 7 observed). SIRs for stomach cancer were 0.91 (95% CI: 0.25-2.3; 4 cases) for high exposure and 3.0 (95% CI: 1.2-6.1; 7 cases) with a 20-year latency. SIRs for prostate cancer were 0.68 (95% CI: 0.08-2.4; based on only 2 cases) for the high-exposure group, and, with a 20-year latency period, 3.6 (95% CI: 1.5-7.0; 8 cases) for the whole cohort (Anttila et al. 1995).

The third key cohort analysis was of 14,066 civilian employees (12,538 white, 1528 of unknown race) who had worked for at least 1 year at a US airforce base between January 1952 and December 1956, maintaining and cleaning aircraft, missiles and parts thereof. Between 1939-1954, the main metal-cleaning solvents were Stoddard solvent, carbon tetrachloride, TCE and alcohols. In 1955, TCE replaced Stoddard solvent, and was itself replaced in 1968 by

1,1,1-trichloroethane. TCE was the primary solvent used in vapour degreasing from 1939-1979, when it was replaced by 1,1,1-trichloroethane (Spirtas et al. 1991). Within the cohort, 10,256 were classified as having been exposed to mixed solvents, 7282 to TCE, 6977 to Stoddard solvent and 6737 to carbon tetrachloride (Stewart et al. 1991). Actual exposure levels were not quantified but, for each combination of job and organization, an index of TCE exposure was calculated on the basis of the frequency of exposure, the frequency of peak exposure and duration of use. Cumulative exposure categories were derived by multiplying the exposure index assigned to each combination of job and organization by the time spent in this job and by adding these products. The workers were followed up until December 1982 (97% were successfully traced), by when 3832 had died, giving (based on Utah cancer rates) an overall SMR of 0.92 (95% CI: 0.90-0.95). Among white men exposed to TCE, there were 1508 deaths (SMR = 0.92; 95% CI: 0.87-0.96), 248 of which were from cancer (SMR = 0.92; 95% CI: 0.81-1.1). For TCE-exposed men and women combined, there were 1694 total deaths (SMR = 0.90; 95% CI: 0.86-0.95) and 281 cancer deaths (SMR = 0.88; 95% CI: 0.78-0.99), and an increased cancer risk for the biliary passages (SMR = 2.2; 95% CI: 0.96-4.4). There were also elevated cancer mortality risks for bone in men (SMR = 2.6; 95% CI: 0.54-7.7; 3 deaths), and for cervix (SMR = 2.2; 95% CI: 0.61-5.7; 4 deaths) and for non-Hodgkin's lymphoma (SMR = 2.9; 95% CI: 0.78-7.3; 4 deaths) in women. There were two deaths from primary liver cancer (SMR = 1.1; 95% CI: 0.12-4.0). No evidence of a dose-response relationship was seen when the data were analysed by cumulative TCE exposure (scored as categories of < 5, 5-25, > 25) for cancer at any site, including cancer of the biliary passages (SMRs were 2.5, 4.3 and 1.3 for low, medium and high exposure respectively; based on 3, 3 and 2 deaths, respectively). Both deaths from liver cancer occurred among men in the lowest category of cumulative exposure (Spirtas et al. 1991).

IARC described a fourth cohort study as “less relevant”, as only about one third of the jobs entailed TCE exposure and worker exposure could not be categorized. The cohort of 14,067 persons who had worked for at least 4 years at a US aircraft manufacturing company between January 1958 and December 1982 was followed up through 1982. Persons lost to follow-up were included up to the last date at which they were known to be alive, and both County and US national rates were used to calculate the expected numbers of deaths. Data from a relatively small case-control study nested in the cohort indicated that 37% of the jobs held in the plant entailed TCE exposure. There were 1804 deaths (SMR = 0.75; 95% CI: 0.72-0.79), of which 453 were cancer deaths (SMR = 0.84; 95% CI: 0.77-0.93). None of the SMRs for individual cancer sites was significantly elevated. There were eight deaths from cancer of the biliary passages and liver (SMR = 0.94; 95% CI: 0.40-1.9) (Garabrant et al. 1988).

The IARC monograph also assessed other, more limited worker cohort studies (Barret et al. 1984; Henschler et al. 1995; Shindell and Ulrich, 1985; Tola et al. 1980) as well as a number of case-control studies (Fredriksson et al. 1989; Hardell et al. 1981, 1984; Heineman et al. 1994; Hernberg et al. 1984, 1988; Lowengart et al. 1987; Olsson and Brandt, 1980; Peters et al. 1981, 1984; Sharpe et al. 1989; Siemiatycki, 1991) that did not offer any clear additional insights into TCE’s cancer potential in man (IARC, 1995).

Although limited in nature, IARC also reviewed a small number of investigations into cancer in populations exposed to TCE in the drinking water. These studies were difficult to interpret because concentration data were obtained either during (or subsequent to) the period in which

cancer occurrence was measured, exposure data related to the community rather than to the individuals, populations tend to migrate in and out of study areas, and potential confounding effects (socioeconomic, industrial and cultural factors were mentioned) were not taken into account. Nevertheless, these are included here for their, albeit limited, contribution towards the picture for human cancer and oral exposure to TCE.

There were no differences in average annual (1969-1981) age-adjusted incidences of bladder, breast, lung, prostate, colon or rectal cancer in towns in Iowa (US) where the TCE concentration in the drinking water was at least 0.15 μg/L, compared with towns where the TCE concentration was lower (Isacson et al. 1985).

The 20 cases of childhood leukaemia diagnosed between 1964-1983 in a US community where water from two wells had been contaminated with TCE (in 1979, TCE was measured at 267 μg/L) were said to be "associated with a significantly higher estimated cumulative exposure to water from the two contaminated wells than [for] a random sample of children from the community (observed cumulative exposure, 21.1; expected cumulative exposure, 10.6; $p = 0.03$)" [IARC phrasing] (Lagakos et al. 1986).

A significantly higher incidence (relative risk (RR) = 1.4; 95% CI: 1.1-1.9) of leukaemia was seen in women from six towns in New Jersey (US) where the water supply contained TCE at above 5 μg/L (mean 23.4, maximum 67 μg/L) than in towns where TCE was present at below 0.1 μg/L. No extra risk was seen in men (RR = 1.1; 95% CI: 0.84-1.4). The women had elevated risks particularly of acute lymphocytic leukaemia, chronic lymphocytic leukaemia and chronic myelogenous leukaemia. The risk of acute lymphocytic leukaemia in childhood was significantly increased in girls but not boys. Increased risk for non-Hodgkin's lymphoma was apparent in towns in the "highest category" [not described further by IARC] of TCE contamination (RR = 1.2; 95% CI: 0.94-1.5 for men; RR = 1.4; 95% CI: 1.1-1.7 for women). This study was carried out during 1979-1987 and included 75 towns. TCE analyses were performed in 1984-1985 (Cohn et al. 1994; Fagliano et al. 1990).

No increases in cancer risk were found in two community studies carried out in Arizona. One was designed to address the possible relationship between TCE-contaminated drinking water and childhood leukaemia, the other all childhood neoplasms and testicular cancer. In one study, two wells that were used occasionally to supplement the drinking water supply were found to contain TCE at 8.9 and 29 μg/L, in 1982, after which they were decommissioned (Flood et al. 1990). In the other, TCE was found at 1-239 μg/L, and up to 4600 μg/L in wells near an airforce base (Arizona Department of Health Services, 1990).

Finally, there was no clear evidence of any increased cancer risk (total, liver or lymphohaematopoietic) in two Finnish villages where the groundwater was contaminated with TCE at up to 212 μg/L (as well as tetrachloroethylene at up to 180 μg/L). Based on analyses of samples obtained from 116 residents, mean urinary excretion of TCA was 19 and 7.9 μg/day in residents of these two villages, respectively, compared with 2 and 4 μg/day in their respective control groups [not defined further by IARC]. There was a marginal excess of non-Hodgkin's lymphoma in one village (SIR = 1.4; 95% CI: 1.0-2.0; 31 cases) but not in the other (SIR = 0.6; 95% CI: 0.3-1.1; 14 cases) (Vartiainen et al. 1993).

IARC concluded that the three most informative studies (Anttila et al. 1995; Axelson et al. 1978, 1984, 1994; Spirtas et al. 1991) consistently indicated an excess relative risk for cancer of the liver and biliary tract, with a total of 23 observed cases, whereas 12.87 were expected. No increase in risk for these cancers was seen in the fourth, more limited cohort study (Garabrant et al. 1988). In two studies (Anttila et al. 1995; Spirtas et al. 1991), risks for liver cancer were reported separately, and these observed a total of 7 cases compared with 4.0 expected (IARC, 1995). Three of the case-control studies also indicated an elevated liver cancer risk in people exposed to solvents, but only a few of the subjects in each study reported TCE exposure. The three most informative cohort studies (Anttila et al. 1995; Axelson et al. 1978, 1984, 1994; Spirtas et al. 1991) also were consistent in showing a modest increase in risk of non-Hodgkin's lymphoma, with a total of 27 cases and 18.9 expected. Again, no increase in risk was seen in the fourth cohort study (Garabrant et al. 1988). The elevated risks in liver and biliary tract cancer, and in non-Hodgkin's lymphoma, in all three of the most informative cohort studies were considered by IARC to be the most important observations. IARC also noted that some of the available studies had reported increased risks in other cancers, including cervix, kidney, urinary bladder and leukaemia, but no clear conclusions were reached for these (IARC, 1995).

4.2 Cancer epidemiology (1995-2009)

4.2.1 General

Since 1995 many more studies have been published that investigated the potential association between TCE exposure and cancer occurrence. These studies had different designs, but were generally comparable to those included in the IARC evaluation: case-control and cohort studies. The cohort studies included updates of investigations included and evaluated by IARC (1995), but also some new studies. A Danish cohort study is of particular interest (Hansen et al. 2001). For the exposure assessment component of these studies, different approaches have been taken. In case-control studies, exposure has been characterized by making use of questionnaires or job exposure matrices. A specific problem with general population case-control studies is that exposures other than to TCE are always a feature and adjustment for such other exposures is not reliable. Although several case-control studies gave results indicative of an association between certain cancer types and TCE exposure, confounding by other exposures cannot be excluded because of the crude exposure characterization and classification. Exposure is characterized by the use of questionnaires or job exposure matrices, and this will result in relatively crude categorizations, even when the exposure is specifically characterized on the individual level. In addition, residual confounding cannot be excluded for those studies in which adjustments would have been made, although generally this has not been done. Therefore, case-control studies were excluded from the more in-depth evaluation of the literature in this report, based on the same arguments applied by IARC. Cohort studies included working populations with usually specific and relatively high exposure to TCE. Although there may have been other exposures in these studies also, the studies used either very specific measured markers of exposure (urinary TCA metabolite specific for TCE exposure), or other exposures were characterized on the individual or group level, making it likely that adjustments made in multivariable analyses were effective. Only cohort studies with well-characterized TCE exposures were used to assess the evidence for

the carcinogenicity of TCE. Because of methodological issues, it was considered that other designs added little to the available evidence. This follows the approach applied earlier by IARC (1995). The studies presented have been stratified by exposure assessment methodology.

4.2.2 Exposure evaluated by biological monitoring

Hansen et al. (2001) studied a cohort of 803 Danish workers who had been exposed to TCE. Exposure was assessed using historical files of individual air measurements of TCE (89 workers), urinary measurements of TCA (712 workers), or both sets of measures (2 workers) over a period of time. These workers were part of a progam where, since 1947, the Labor Inspection Services in Denmark had performed individual measurements of persons exposed to TCE. Not all TCE-exposed worker were monitored, there being different reasons for initiation of monitoring (e.g. routine measurements, specific campaigns on hazardous substances, or requests from doctors, employers or employees due to concerns over exposure or following accidents). During the period 1947 to 1989, a total of 2397 samples were analyzed for the TCE-metabolite TCA in the urine of exposed persons at 275 different companies. Since 1974, a total of 472 measurements of TCE in individuals' breathing zones were also performed at 81 different companies. For both, records were kept at the National Institute of Occupational Health (Hansen et al. 2001). Results from the TCA urine measurements have been published separately (Raaschou-Nielsen et al. 2001). The mean and median concentrations of urinary TCA for the entire period were 40 and 15 mg/L, respectively. Corresponding figures for air measurements (1974 to 1989) were 101 and 28 mg/m^3. The calculated mean and median air concentrations of TCE (after transforming the urinary-TCA measurements to air concentrations; thus, air- and urinary- TCA measurements together) were 65 mg/m^3 (TCA = 34 mg/L) and 19 mg/m^3 (TCA = 10 mg/L), respectively. A regression analysis showed a four-fold decrease in TCA concentration over time between 1947 and 1985. Highest concentrations were observed in the iron and metal, chemical, and dry cleaning industries and TCA levels were twice as high among men compared with women in the iron and metal and dry cleaning industries. TCA concentrations were higher among younger workers compared to older workers. Also, bystander exposure was observed since persons working in an area in which TCE was used, but who did not work with TCE themselves, had detectable urinary TCA levels indicative of exposure. These data strongly support the exposure categorization applied in the cohort studies and give quantitative information about exposure levels and trends of exposure. This makes this one of the better-documented studies from the perspective of exposure information for the period since the IARC review. No information on start and end dates for jobs involving TCE exposure was available from the measurements files. Job information was reconstructed from the files of the national Pension Fund using the personal identification number, company name and dates of exposure. The employment history was identified from the Pension Fund files for 654 (of 662) workers with measurements from 1964 or later. For the remaining 149 persons (19%), only the measurement dates before 1964 were available. The period of follow-up for cancer occurrence began on the later of 1 April 1968 or the date of first employment. Unknown dates of employment were replaced with the first date of monitoring (after 1 April 1968). Follow-up ended on the date of death, emigration, or 31 December 1996, whichever occurred first. Danish national incidence rates were used for the calculation of expected numbers of site-specific

cancers by sex, 5-year age group, and calendar year. Each person was categorized according to period of first employment (pre-1965 or 1965 and later) and duration of employment (< 75 and > 75 months). Further, each person was grouped according to the mean air concentration of TCE (19 mg/m^3) and if duration of employment was available, also to the calculated median (1080 months.mg/m^3) cumulative exposure. Persons who ended employment before the establishment of the Pension Fund in 1964, and for whom a duration period could not be calculated, were categorized separately. A total of 246 cohort members (21%) died during follow-up (Hansen et al. 2001).

The standardized incidence ratio (SIR) for cancer overall was close to unity for both men and women exposed to TCE. Men had significantly elevated SIRs for non-Hodgkin's lymphoma (SIR = 3.5; 95% CI: 1.5-6.9; 8 observed) and cancer of the oesophagus (SIR = 4.2; 95% CI: 1.5-9.2; 6 observed). This increase was unlikely to be due to alcohol intake, as only one of the six cases was a squamous cell carcinoma (the main type associated with alcohol); the other five were adenocarcinomas. Men also had a non-significantly elevated SIR for cancer of the liver and biliary passages (SIR = 2.6; 95% CI: 0.8-6.0; 5 observed). Among women, the SIR for cervical cancer was significantly increased (SIR = 3.8; 95% CI: 1.0-9.8; 4 observed), but the investigators concluded that this could probably be attributed to a lack of control of social class in the analysis. The main cause of cervical cancer (human papilloma virus) is strongly associated with social class. The limited number of cases available for analysis did not allow exposure response modeling, latency analysis or time window analysis. Trends with duration or level of exposure were considered in a qualitative way considering descriptive information for non-Hodgkin's lymphoma, oesophageal cancer and cervical cancer. This qualitative evaluation did not reveal any clear dose-response relationship for any of these cancers, based on estimates of individual exposure level or cumulative exposure. For non-Hodgkin's lymphoma and cancer of the oesophagus, a tendency of increasing duration of employment was apparent but neither trend was statistically significant because of low numbers of cases. Again, the absolute numbers of cancers included for these sites was small; 8 for non-Hodgkin lymphoma and 6 for cancers of the oesophagus. No increase in kidney cancer risk was seen, but the number of cases (4) was very small (Hansen et al. 2001).

4.2.3 Exposure evaluated by job exposure matrices

Morgan et al. (1998) studied mortality rates in a cohort of 20,508 aerospace workers who were employed at the facility for at least 6 months and followed up from 1 January 1950 to 31 December 1985. This cohort had been evaluated before, but the results were published in a report and not in the peer-reviewed literature (ENSER Health Sciences, 1990). The cohort included 13,742 male and 6766 female workers, of whom 18,830 were white and 1678 non-white. A total of 4733 workers had been occupationally exposed to TCE (2555 males, 2178 females; 4132 white, 601 non-white). TCE was present in some of the washing and drinking water used at the work site but potential exposure from these sources was not considered in classifying occupational exposure.

A job-exposure matrix was used to classify all jobs by TCE exposure into four categories ranging from high, medium, low and no exposure as a base, to arrive at a cumulative exposure score. This job exposure matrix was based on limited measurements (not further described) by the facility's occupational hygienists, and this was reviewed with and confirmed by employees. The high exposure category involved working on degreasing machines and exposure levels above 50 ppm (averaging times not given). In the SMR analysis, cumulative exposure scores were used with a dichotomous measure to define exposure groups. SMRs were calculated for the entire cohort and the TCE-exposed subcohort. A consistent elevation was observed for non-malignant respiratory disease, which was attributed primarily to the higher background rates of respiratory disease in that region. TCE-exposed workers were also compared with workers in the "low" and "none" exposure categories.

There were elevated rate ratios for ovarian cancer among those with peak exposure to TCE at medium/high levels (relative risk (RR) = 2.74; 95% CI: 0.84-8.99) and among women with high cumulative exposure (RR = 7.09; 95% CI: 2.14-23.54). Among those with peak exposures at medium/high levels, slightly elevated rate ratios were seen for cancer of the kidney (RR = 1.89; 95% CI: 0.85-4.23), bladder (RR = 1.41; 95% CI: 0.52-3.81) and prostate (RR = 1.47; 95% CI: 0.85-2.55). There was no evidence of an association between TCE exposure and respiratory cancer, liver cancer, leukaemia or lymphoma, or all cancers combined (Morgan et al. 1998).

Ritz (1999) studied mortality rates in a cohort of 3814 white male uranium-processing workers employed at the Fernald Feed Materials Production Center (FFMPC) in Fernald, Ohio. Workers processed uranium-ore concentrate and uranium of low-enrichment grade into fabricated uranium metal products and, to a much lesser extent, produced thorium metal. Operations began in late 1951 and halted in July 1989. The uranium-processing work conducted at this facility involved the use of large amounts of non-radioactive industrial chemicals (hydrofluoric acid, ammonia, nitric and sulphuric acid, tributyl phosphate, TCE and cutting fluids). Workers were followed-up from 1 January 1951 or date of hire (whichever date was later) until death or 31 December 1989 (whichever date came earlier). Employees were identified from company rosters and personnel records. Vital-status searches were conducted using two record systems: the Social Security Administration, for the period before 1979, and the National Death Index, for the period 1979 to 1989. Workers not known to be alive and not identified by either system as dead were assumed to be alive at the end of follow-up. Death-certificate information was available for a total of 1045 workers who died during the follow-up period. Mortality data for FFMPC workers are only available in the CEDR database for those workers who were radiation-monitored. Plant experts, who had been at the company for at least 20 years (including industrial hygienists, a plant foreman, and an engineer) determined historically for the late 1970s and early 1980s the likelihood of chemical exposure for each job title and plant area. For the period 1952 to 1977, these experts classified workers into four main categories of chemical exposure, from none to heavy. For the analyses, measures of intensity (exposure level) and duration (exposure in years) were derived from the job-exposure matrix created by the plant expert to describe exposure to TCE, cutting fluids, and kerosene. Expected numbers of deaths were estimated from the mortality rates of the US white male population or NIOSH-CORPS data, stratified by age (5-year categories) and calendar year (5-year intervals). They estimated the effects of exposure to TCE, cutting fluids and kerosene on cancer mortality. The overall mortality rate was lower among

Fernald workers than among US white males (SMR = 0.84; 95% CI: 0.79-0.90); however, the rate of deaths from all cancers was slightly increased (SMR = 1.10; 95% CI: 0.99-1.23).

When the uranium-worker cohort was compared with NIOSH-CORPS workers, the SMR for all causes was still lower (SMR = 0.81; 95% CI: 0.76-0.86) but the cancer mortality rate was even higher (SMR = 1.24; 95% CI: 1.11-1.38) among the uranium workers. Compared with the US population, the SMRs for the Fernald cohort exceeded unity (though not to a statistically significant extent) for cancers of all digestive system organs, the prostate, and the lymphopoietic system. TCE exposure was strongly associated with liver cancer (exposure duration > 5 years; 15-year lag RR = 12.1; 95% CI: 1.03-144). TCE exposure seemed also to be associated with brain cancers in the analyses of single chemicals, but this effect disappeared completely when cutting-fluid exposure was included in the model (Ritz, 1999).

Boice et al. (1999) retrospectively studied a cohort of 77,965 workers employed for at least 1 year at the Lockheed Martin aircraft manufacturing factories in California on or after 1 January 1960. Workers employed for less than 1 year were excluded. Workers were followed up between 1 January 1960 and 31 December 1996, accruing nearly 1.9 million person-years of follow-up (mean 24.2 years). The mortality follow-up was estimated as 99% complete and 20,236 workers had died by 31 December 1996, with cause of death obtained for 98%. The cohort was 80.1% male and 90.7% white. Work history cards, personnel files, and retirement records were used to identify the worker population. Workers were potentially exposed to compounds containing chromate, TCE, perchloroethylene (PCE), and mixed solvents. Exposure was assessed by walkthrough surveys, interviews with active and retired workers, existing industrial hygiene files and other historical documents. This information was used to identify job “families” and job titles. Individual workers were then classified into categories of routine, intermittent, or no likely exposure to chromate, TCE, PCE and mixed solvents, and the duration of exposure to each substance was determined. The mortality experience of these workers was determined by examination of national, state and company records to the end of 1996. The SMRs for 40 causes of death categories were computed for the total cohort and for subgroups defined by sex, race, factory job, work duration, year of first employment, latency, and broad occupational groups. Factory job titles were classified with regard to likely use of chemicals, and internal Poisson regression analyses were used to compute mortality risk ratios for categories of years of exposure to chromate, TCE, PCE and mixed solvents, with unexposed factory workers serving as referents.

The SMR of all causes of death was 0.83 (95% CI: 0.82-0.84; 20,236 deaths) and the SMR for cancer mortality was 0.90 (95% CI: 0.88-0.92; 5468 deaths). The study showed no significant increases in risk for any of the 40 causes of death categories, and for several causes the numbers of deaths were significantly below expectation. No remarkable mortality patterns were seen in analyses by occupational group and specific job titles. There were no significant increases in any cause of death among workers who were potentially exposed to TCE on a routine basis (n = 2,267; 66,183 person-years), and the SMR for all causes of death was 0.83 (95% CI: 0.79-0.88; 1110 deaths) and for all cancer was significantly lower (SMR = 0.86; 95% CI: 0.76-0.97; 277 deaths). Deaths due to non-Hodgkin's lymphoma among workers exposed to TCE were slightly above expected numbers, but not significantly so (SMR = 1.19; 95% CI: 0.65-1.99; 14 observed). Liver cancer risk was lower, but not significantly so (SMR = 0.54; 95% CI: 0.15-

1.38; 4 observed). The SMRs for the workers with any potential routine or intermittent exposure to TCE were similar to those workers with daily potential exposure: all cancers SMR = 0.86 (95% CI: 0.79-0.92), liver SMR = 0.81 (95% CI: 0.45-1.33) and non-Hodgkin's lymphoma SMR = 1.19 (95% CI: 0.83-1.65) (Boice et al. 1999).

Radican et al. (2008) reported on the extended follow-up of 14,455 workers of the Hill Air Force Base cohort from 1990-2000 who had worked for at least 1 year at an air force base in Utah, US, between 1 January 1952 and 31 December 1956. This cohort had been studied previously (Blair et al. 1998; Spirtas et al. 1991) and included in the IARC (1995) review. The cohort included 10,730 male and 3725 female workers, of whom 12,537 were white, 390 non-white and 1528 of unknown race. At the end of follow-up (31 December 2000), 8580 workers had died, adding 2853 deaths to those analysed in the 1990 follow-up (Blair et al. 1998). The frequency and pattern of TCE exposure were based on the job tasks. Four categories of TCE exposure were used, low intermittent, low continuous, peak infrequent, and peak frequent. Estimates of the frequency, duration and intensity for TCE exposure were developed and from these a cumulative exposure score for each worker in each job, summed across all jobs, was derived. The overall Cox Model Hazard Ratio (HR) of all-cause mortality in the cohort was 1.04 (95% CI: 0.98-1.09; 4320 deaths) and of death from all cancers 1.03 (95% CI: 0.91-1.17; 854 deaths). No increased risk of death from all causes or all cancers was observed. Among men exposed to TCE, there were 1287 deaths (HR = 1.09; 95% CI: 1.01-1.18), 249 of which were from cancer (HR = 1.13; 95% CI: 0.94-1.36). Among women exposed to TCE, there were 349 deaths (HR = 1.00; 95% CI: 0.88-1.13), 58 of which were from cancer (HR = 0.86; 95% CI: 0.64-1.16). Non-significant excess risks among men were found for cancer of the liver (HR = 2.72; 95% CI: 0.34-21.88; 8 observed) and among women for multiple myeloma (HR = 2.37; 95% CI: 0.67-8.44). Overall there were eight deaths from primary liver cancer (HR = 1.25; 95% CI: 0.31-4.97). Deaths from liver cancer occurred only among men in the lowest and highest categories of cumulative TCE exposure.

There was some evidence of an exposure-response gradient by tertile of cumulative TCE exposure score in men for death from all causes; 0-5 units years: HR = 1.00 (95% CI: 0.92-1.08; 1419 deaths), 5-25 units years: HR = 1.05 (95% CI: 0.97-1.15; 922 deaths) and >25 units years: HR = 1.09 (95% CI: 1.01-1.18; 1287 deaths), primary liver cancer 0-5 units years: HR = 3.28 (95% CI: 0.37-29.45; 4 observed), 5-25 units years (could not be calculated due to empty cells) and >25 units years: HR = 4.05 (95% CI: 0.45-36.41; 4 observed), cancer of the lymphatic or haematopoietic system 0-5 units years: HR = 1.04 (95% CI: 0.63-1.74; 34 observed), 5-25 units years: HR = 1.06 (95% CI: 0.59-1.88; 21 observed) and >25 units years: HR = 1.25 (95% CI: 0.75-2.09; 33 observed), Hodgkin’s disease 0-5 units years: HR (could not be calculated due to empty cells), 5-25 units years: HR = 2.27 (95% CI: 0.21-25.01; 2 observed) and >25 units years: HR = 2.59 (95% CI: 0.27-24.94; 3 observed). Exposure-response gradients for TCE were relatively weak and flat and had not changed substantially since the last follow-up of this cohort in 1990 (Radican et al. 2008).

Zhao et al. (2005) retrospectively studied a cohort of 6107 male workers who had been employed before 1980 in the aerospace division of the SSFL between 1950 and 1993, and examined cancer mortality from exposures to the rocket fuel hydrazine. Workers had to have worked for at least 2 years at any Rockwell/Rocketdyne facility and never been monitored for radiation exposure.

These workers had worked during the most active period of rocket engine testing but were never employed at the nuclear facilities also housed at the SSFL. The source population for this cohort consists of 55,000 workers employed between 1950 and 1993 at several Boeing North America (formerly Rockwell/Rocketdyne) facilities in Los Angeles. Mortality information, including date of death and underlying and contributing causes of death, were obtained from multiple sources (company records, Social Security Administration beneficiary files, vital statistics files for California, and the US National Death Index. A job exposure matrix (JEM) was used to assess exposures to other known or suspected carcinogens, including TCE, polycyclic aromatic hydrocarbons (PAHs), mineral oils and benzene, and effects on cancer mortality (1960-2001) and incidence (1988-2000). Company records provided job titles, job codes, and dates of employment for each worker, and this information was linked to the JEM to generate a time-dependent intensity score for each occupational chemical exposure and worker. Rate-(hazard-) ratio estimates from Cox proportional hazard models with time-dependent exposures were derived. High levels of TCE exposure were positively associated with the incidence of kidney cancer (RR = 4.90; 95% CI: 1.23-19.6; 4 observed). The association between TCE exposure and kidney cancer mortality was weaker than for incidence in both single (RR for high exposure levels at zero lag = 2.03; 95% CI: 0.50-8.32; 3 observed) and multi-chemical models. TCE exposure was also associated with bladder cancer (RR for high exposure levels at zero lag = 1.98 (95% CI: 0.93-4.22; 11 observed). No associations were observed between TCE exposure and other cancers in this cohort (Zhao et al. 2005).

4.2.4 Exposure evaluated by job histories

Raaschou-Nielsen et al. (2003) evaluated cancer incidence in a cohort of 40,049 blue-collar workers employed for more than 3 months in at least one of 347 Danish companies with documented TCE use between 1968 and 1997. The period of follow-up for cancer occurrence began on 1 April 1968 or the date of first employment, whichever occurred later. Follow-up ended on the date of death, emigration, or 31 December 1997, whichever occurred first. Danish national incidence rates were used for the calculation of expected numbers of site specific cancers by sex, 5-year age group, and calendar year.

Exposure was assessed based on an earlier study of Raaschou-Nielsen et al. (2001), using three variables that seemed the most reliable predictors of TCE exposure (duration of employment, year of first employment at a TCE-using company, and the number of employees in the company). TCE exposure was expected to be 4-5 times higher in the 1960s than in the 1980s. The proportion of exposed workers was expected to be about four times higher in smaller than in larger companies. SIRs were calculated within different strata of duration of employment (< 1 year, 1-4.9 years, ≥ 5 years), first year of employment (before 1970, 1970-1979, 1980 and later), and number of employees in the company or companies where the worker had been employed (< 50, 50-99.9, 100-200). The latter variable was calculated as a time-weighted average over the actual follow-up period of each worker.

Overall, SIRs for cancer were 1.08 (95% CI: 1.04-1.12; 2620 observed) in men and 1.23 (95% CI: 1.14-1.33; 624 observed) in women. For non-Hodgkin's lymphoma the SIR in men was 1.2

(95% CI: 0.98-1.52; 83 observed) and in women 1.4 (95% CI: 0.73-2.34; 13 observed). For kidney cancer the SIR in men was 1.2 (95% CI: 0.97-1.48; 93 observed) and in women 1.2 (95% CI: 0.55-2.11; 10 observed), SIRs increased with duration of employment, and elevated SIRs were limited to workers first employed before 1980 for non-Hodgkin's lymphoma and before 1970 for renal cell carcinoma. The SIR for oesophageal adenocarcinoma in men was 1.8 (95% CI: 1.15-2.73; 23 observed), and higher in companies with the highest probability of TCE exposure. In a sub-cohort of 14,360 presumably highly-exposed workers (both sexes combined), the SIRs for non-Hodgkin's lymphoma, renal cell carcinoma, and oesophageal adenocarcinoma were 1.5 (95% CI: 1.2-2.0; 65 observed), 1.4 (95% CI: 1.0-1.8; 53 observed), and 1.7 (95% CI: 0.9-2.9; 13 observed), respectively, the latter two being on the borderline of statistical significance (Raaschou-Nielsen et al. 2003).

Boice et al. (2006) studied a retrospective cohort of 8372 Rocketdyne workers employed from 1948 to 1999 at the Santa Susana Field Laboratory (SSFL) on or after 1 January 1948, for at least 6 months. Rocketdyne workers employed at nearby facilities (n = 32,979) were also included as an additional comparison group. Workers who worked for less than 6 months (n = 6601), workers with missing or inadequate work histories and identifying information (n = 289), not Rocketdyne workers (n = 524), and workers engaged in radiation work (n = 5619) were excluded. Test stand mechanics monitored for radiation (n = 182) were included because of the relatively small numbers available for study (n = 1651). Workers were followed up between 1 January 1948 and 31 December 1999, and 228 workers (0.6%) were lost to follow-up. The cohort was 77.0% male and 75.6% white. Overlapping record sources such as work history cards, computerized personnel files, and available retirement records were used to identify the worker population. Mortality was determined from the California death tapes (1960-1999), California death index (1940-1960), National Death Index (1979-1999), Pension Benefit Information files, Social Security Master File, the Health Care Financing Administration beneficiary files, employment work history cards, pension records, and retirement records. The job title entries on the job history cards (n > 73,000) and the electronic personal file (n > 275,000) were collapsed into job title categories and each job category was designated as administrative/scientific or non-administrative. Workers and in particular test stand mechanics were potentially exposed to a wide range of rocket fuels, oxidizers, exhaust gases, solvents and other chemicals. TCE was used to clean (flush) engines and as a utility solvent to clean small metal parts. External comparisons contrasted the observed number of deaths with that expected in the general population of California and in the general population of the United States. Observed numbers of deaths from cancers and all other diseases were determined by race, gender, age, and calendar year for workers overall and for subgroups defined by time since first exposure, duration of employment, work location, job title, and potential exposure to hydrazines and TCE. The SMR for all causes of death in the SSFL cohort was 0.83 (95% CI: 0.80-0.86; 2251 deaths) and for cancer mortality was 0.89 (95% CI: 0.82-0.96; 655 deaths) and test stand mechanics in particular (SMR = 1.00; 95% CI: 0.86-1.16; 1651 deaths), including those likely exposed to hydrazines (SMR = 1.09; 95% CI: 0.75-1.52; 315 deaths) or TCE (SMR = 1.00; 95% CI: 0.83-1.19; 1111 deaths). No significant trends or significant relative risks were seen for the 1111 test stand mechanics with potential exposure to TCE for any category of years of potential exposure to any TCE (engine flush and/or utility solvent) for all cancers taken together (p for trend = 0.56), lung cancer (p for trend = 0.69), or kidney cancer (model did not converge). There were also no significant trends for these cancers among the 518 workers with potential TCE

exposure during the flushing or cleaning of engines using the weighted measure of exposure that took into account the number of tests performed during a specific year at a specific test area and the number of workers assigned to that same area: for all cancers (p for trend = 0.56), lung cancer (p for trend = 0.69) or kidney cancer (p for trend = 0.59). There was a suggestion of a positive dose-response for kidney cancer, but it was not significant and based on only four deaths among those with potential exposure to TCE during engine flush. Cancers of the liver and non-Hodgkin's lymphoma also showed no significantly increased risks. In conclusion, work at the SSFL rocket engine test facility or as a test stand mechanic was not associated with a significant increase in cancer mortality overall or for any specific cancer (Boice et al. 2006).

4.3 Laboratory animal cancer overview (up to 1995)

4.3.1 IARC overview

In two adequate oral studies in mice, TCE induced benign and malignant liver tumours. Most of the seven oral TCE studies in rats were inconclusive (because treatment time was too short or survival was reduced), but two studies found increases in uncommon benign and malignant renal-cell tumours in males, and one study reported an increase in interstitial testicular tumours (IARC, 1995).

Increases in benign and malignant lung tumours were seen in three of the four inhalation studies in mice, and malignant liver tumours or lymphomas were increased in individual studies. In one of the three rat inhalation studies, the males showed an increase in interstitial testicular tumours and a marginal increase in malignant renal-cell tumours. No evidence of carcinogenic activity was seen in hamsters exposed to TCE by the inhalation route (IARC, 1995).

In limited studies involving topical application or subcutaneous injection, TCE or a proposed metabolite (TCE-oxide) did not increase skin tumour or local sarcoma incidence in mice (IARC, 1995).

These studies are described in a little more detail in following sections, and are summarized in Tables 3 and 4.

4.3.2 Oral studies – Mouse

TCE (purity > 99%; containing 0.19% epoxybutane and 0.09% epichlorohydrin [see IARC, 1987] as stabilizers) was given in corn oil to 5-week-old B6C3F1 mice (50/sex/group in treated groups, 20/sex in vehicle control group) by gavage on 5 days/week for 78 weeks, giving time-weighted average TCE doses of 0, 1169 and 2339 mg/kg bw/day for males and 0, 869 and 1739 mg/kg bw per day for females. Mice were killed 90 weeks after treatment started and a "complete" necropsy and histopathological evaluation was undertaken. Survival figures were 8/20, 36/50 and 22/48 in the control, low-dose and high-dose males; the equivalent figures for

females were 20/20, 42/50 and 39/47. The survival-adjusted (Cox and Tarone test) incidences of hepatocellular carcinomas were increased in animals of each sex in relation to dose; males: l/20 in controls, 26/50 ($p = 0.004$) at the low dose, 31/48 ($p < 0.001$) at the high dose; females: 0/20 in controls, 4/50 at the low dose, 11/47 ($p = 0.008$) at the high dose. One male at the high dose developed a forestomach papilloma (NCI, 1976).

In a subsequent study, TCE (purity > 99.9%; 8 ppm amine, no epichlorohydrin) was given in corn oil to 8-week-old B6C3FI mice (50/sex/group) at 0 or 1000 mg/kg bw/day by gavage on 5 days/week for up to 103 weeks. Survival of treated males was significantly reduced ($p = 0.004$); 33 control and 16 treated males and 32 control and 23 treated females were alive at the end of the study. Treated mice had increased incidences (incidental tumour test) of liver tumours. In males, incidences in control and treated groups were, respectively, 7/48 and 14/50 ($p = 0.048$) for hepatocellular adenomas; 8/48 and 31/50 ($p < 0.001$) for hepatocellular carcinomas; and 14/48 and 39/50 ($p < 0.001$) for combined hepatocellular adenomas and/or carcinomas. The equivalent figures in females were 4/48 and 16/49 ($p = 0.001$) [adenomas], 2/48 and 13/49 ($p = 0.002$) [carcinomas], and 6/48 and 22/49 ($p < 0.001$) [adenoma/carcinoma combined]. No significant increases in tumour incidence were found at other tissue sites. Toxic nephrosis (cytomegaly) was seen in 90% of treated males and in 98% of treated females (NTP, 1990).

IARC described the conduct and reporting of a third mouse study as inadequate. A single low dose level was used, dosing was intermittent, and the extent of examination was limited. ICR:Ha Swiss mice (30/sex/group; aged 6-8 weeks) were given 0 or 0.5 mg TCE [purity unspecified] by gavage in 0.1 ml trioctanoin, once/week for at least 74 weeks. Only sections of lung, liver and stomach were examined, and the only reported result was that forestomach tumour incidence was not increased (Van Duuren et al. 1979).

IARC also summarised another, very limited study, where ICR:Ha Swiss mice (50/sex/group) were treated with purified TCE (purity > 99.9%; 0.0015% triethanolamine; no epoxy stabilisers), industrial grade TCE (purity 99.4%; 0.11% epichlorohydrin and 0.20% 1,2-epoxybutane), purified TCE with 0.8% added epichlorohydrin, purified TCE with 0.8% added epoxybutane, or purified TCE with 0.25% added of each stabiliser. The TCE grades were given initially at 1.8 and 2.4 g/kg bw/day (females and males respectively) by gavage in corn oil, on 5 days/week. Due to severe toxicity, dosing was interrupted for several weeks and all doses were reduced by one-half from week 40, up until 18 months, which was followed by a 6-month observation period without further treatment. Survival was reduced in males of all treated groups and females in the groups given purified TCE and purified TCE plus epichlorohydrin. Forestomach tumours were seen, but only in the groups given TCE stabilised with epoxides, which were thus held responsible for these local tumours. Hepatocellular tumours (adenomas and carcinomas combined) occurred in 3/50 controls, 6/50 treated with purified TCE and 9/50 treated with industrial grade TCE (Henschler et al. 1984). IARC noted the absence of a survival-adjusted analysis of tumour incidence (IARC, 1995).

4.3.3 Oral studies – Rat

High mortality rates and a limited treatment duration reduced the value of an NCI study in which TCE (purity > 99%; 0.19% epoxybutane and 0.09% epichlorohydrin as stabilizers) was given to Osborne-Mendel rats (50/sex/treated group; 20/sex vehicle controls; age 6 weeks) in corn oil at time-weighted average TCE doses of 0, 549 or 1097 mg/kg bw/day, by gavage, on 5 days/week for 78 weeks. Rats were killed after 110 weeks and underwent a "complete" necropsy. Survival was low in all groups (3/20, 8/50 and 3/50 control, low- and high-dose males; 8/20, 13/48 and 13/50 control, low- and high-dose females). There were no significant differences in tumour incidence at any tissue site (NCI, 1976)

An increase in uncommon kidney tumours was suggested in a subsequent study, where TCE (purity > 99.9%; 8 ppm amine, no epichlorohydrin) was given at 0, 500 or 1000 mg/kg bw/day in corn oil by gavage on 5 days/week for up to l03 weeks to Fischer 344/N rats (50/sex/group; 8 weeks of age). Survival of treated males was reduced ($p < 0.005$). At the end of the study, there were 35, 20 and 16 male survivors in the control, low- and high-dose groups; equivalent numbers for females were 37, 33 and 26. An increased incidence of renal tubular-cell adenocarcinomas was seen in males: 0/49 untreated controls, 0/48 vehicle controls, 0/49 low dose and 3/49 high dose ($p = 0.028$; incidental tumour test). Two males at the low dose had renal tubular-cell adenomas. There was no evidence of carcinogenicity in the females. Toxic nephrosis of the kidney occurred in 96/98 treated males and in all of the treated females but not in vehicle control rats of either sex (NTP, 1990).

In other NTP studies, TCE (purity > 99.9%; 8 ppm amine, no epoxide) was given at 0, 500 or 1000 mg/kg bw/day, on 5 days/week for 103 weeks, by gavage in corn oil to rats of four strains (ACI, August, Marshall and Osborne-Mendel; 6.5-8 weeks of age). Additional groups (50/sex/strain) served as untreated controls. Untreated and vehicle-treated controls showed no kidney toxicity, but the incidence of renal cytomegaly was > 80% in all treated groups (both sexes), and toxic nephropathy (described as dilated tubules lined by elongated and flattened epithelial cells) occurred at rates of 17-80% in the treated groups. In the Osborne-Mendel rats, survival was unaffected in the treated males (at 18, 22, 17 and 14 of the untreated control, vehicle controls, low-dose and high-dose groups) but reduced in the treated females (19, 18, 10 and 7 survivors in these groups, respectively). The low-dose males showed increased incidences of renal tubular-cell hyperplasia and tubular-cell adenoma (hyperplasia: 0/50, 0/50, 5/50 and 3/50 in untreated control, vehicle control, low-dose and high-dose groups; adenoma: 0/50, 0/50, 6/50 ($p = 0.007$; survival-adjusted incidental tumour test) and 1/50, respectively). One renal tubular-cell adenocarcinoma occurred in a high-dose male Osborne-Mendel rat. In the Marshall rats, survival was reduced in treated groups (males: 32, 26, 12 and 6 survived in the untreated control, vehicle control, low- and high-dose groups; females: 31, 30, 12 and 10, respectively). The incidences of interstitial-cell tumours of the testis were increased in TCE-exposed Marshall rats: 16/46, 17/46, 21/48 ($p < 0.001$; survival-adjusted incidental tumour test) and 32/48 ($p < 0.001$) in the untreated control, vehicle control, low- and high-dose groups, respectively. No significant increases in tumour incidence were reported for ACI or August rats, but survival was generally poor (NTP, 1988).

IARC noted the short duration of a smaller study that involved the gavage treatment of Sprague-Dawley rats (30/sex/group; aged 12-13 weeks), with TCE (purity 99.9%; no epoxide) at 0, 50 or 250 mg/kg bw/day in olive oil, 4-5 days/week, for 52 weeks followed by observation for life. Survival data were not provided, but the authors reported a non-significant increase in mortality among treated females. Renal tubular-cell cytokaryomegaly was observed only in male rats at the high dose (14/30; $p < 0.01$). A non-significant increase in the incidence of leukaemia was observed in males: (0/30, 2/30 and 3/30 in controls, low-dose and high-dose groups, respectively (Maltoni et al. 1986).

4.3.4 Inhalation studies – Mouse

There was evidence of a treatment-related increase in lung tumours in a study where ICR mice (49-50 females/group; 7 weeks of age) were exposed to air containing TCE (purity 99.8%; 0.13% carbon tetrachloride, 0.02% benzene and 0.019% epichlorohydrin) at 0, 50, 150 or 450 ppm (0, 270, 810 or 2430 mg/m^3), 7 hours/day, 5 days/week, for up to 104 weeks. Survival was unaffected and a "complete" necropsy was carried out on all animals. Histopathological evaluation revealed a significant increase (Fisher's exact test) in the incidence of lung adenocarcinomas: 1/49, 3/50, 8/50 ($p < 0.05$) and 7/46 ($p < 0.05$) in the control, low-, mid- and high-dose groups, respectively. IARC found a significant dose-response trend ($p = 0.034$) when applying a Cochran-Mantel-Haenszel test. The mean number of lung tumours/mouse was increased in the mid- and high-dose groups (0.12, 0.10, 0.46 and 0.39 in control, low-, mid- and high-dose groups). However, the incidences of combined lung adenomas and adenocarcinomas at the mid (13/50) and high dose (11/46) were not significantly increased (6/49 in controls) (Fukuda et al. 1983).

A dose-related increase in lung tumour incidence was also reported in females when B6C3F1 mice (90/sex/group; aged 12 weeks) were exposed to TCE (purity 99.9%; no epoxide) at 0, 100, 300 or 600 ppm (0, 540, 1620 or 3240 mg/m^3) in air, 7 hours/day, 5 days/week for 78 weeks and then observed for life. Survival data were not provided, but mortality was reported to be higher ($p < 0.05$) in the treated males. Lung tumour incidence figures in females were: 4/90, 6/90, 7/90 and 15/90 ($p < 0.05$ for high-dose group) in control, low-, mid- and high-dose groups, respectively. There was also a slight increase in hepatoma incidence at the high dose; this increase was statistically significant when males and female were analysed together (combined incidences were 2, 3, 4 and 8% in the control, low-, mid- and high-dose groups, respectively) (Maltoni et al. 1986, 1988).

A similar study in Swiss mice gave evidence of lung and liver cancer activity although, in this strain, the males were the susceptible sex. The mice (90/sex/group; 11 weeks old), inhaled TCE (purity, 99.9%; no epoxide) at 0, 100, 300 or 600 ppm (0, 540, 1620 or 3240 mg/m^3), 7 hours/day, 5 days/week for 78 weeks and were then observed for life. Survival data were not provided. Dose-related increases in lung and liver tumour incidences were observed in males (Fisher's exact test or Cochran-Armitage linear trend test). Lung tumour incidences in males were 10/90, 11/90, 23/90 ($p < 0.05$) and 27/90 ($p < 0.01$) in the control, low-, mid- and high-dose groups, respectively. The equivalent figures for liver adenoma and carcinoma combined in the

males were 4/90, 2/90, 8/90 and 13/90 ($p < 0.05$ for high-dose group), respectively (Maltoni et al. 1986, 1988).

In a limited study, NMRI mice (30/sex/group; age unspecified) were exposed to TCE (purity > 99.9%; 0.0015% triethanolamine; epoxide-free) at 0, 100 or 500 ppm (0, 540 or 2700 mg/m^3) in air, 6 hours/day, 5 days/week for 18 months, followed by a period without exposure until 30 months. At 18 months, treatment had not affected survival of females but, in males, survival was reduced from 83% in controls to 63% in low-dose and 56% in high-dose groups. Histopathological examination of spleen, liver, kidney, lung, heart, stomach, central nervous system and all tumours indicated statistically significant ($p = 0.01$ or better) increases in age-adjusted incidences of lymphomas in treated females: 9/29, 17/30 and 18/28 in controls, low-dose and high-dose groups, respectively (Henschler et al. 1980).

4.3.5 Inhalation studies – Rat

An increase in testicular tumours and a marginal increase in kidney tumours were reported when Sprague-Dawley rats (130-145/sex/group; 12 weeks of age), were exposed to TCE (purity 99.9%; no epoxide) at 0, 100, 300 or 600 ppm (0, 540, 1620 or 3240 mg/m^3) in air, 7 hours/day, 5 days/week for 104 weeks, followed by observation for lifetime. Survival data were not provided. There was a significant, dose-related increase in the incidence of Leydig cell (interstitial) tumours of the testis [$p < 0.001$; Cochran-Mantel-Haenszel test]. The percentages [incidences] of male rats bearing these tumours were 4.4% [6/135], 12.3% [16/130; $p < 0.05$; Fisher's exact test], 23.1% [30/130; $p < 0.01$; Fisher's exact test] and 23.8% [31/130; $p < 0.01$; Fisher's exact test] in the control, low-, mid- and high-dose groups, respectively. Renal tubular adenocarcinomas were seen in four (3.1%) high-dose male rats, compared with none in the lower dose groups, in controls or in the historical control database for Sprague-Dawley rats at the study laboratory. Cytokaryomegaly of renal tubular cells was observed at the mid- and high-dose (in 17 and 78% of the male rats, respectively), but not in control or low-dose rats (Maltoni et al. 1986, 1988).

Gross and histopathological examination [the tissue range was not specified in IARC, 1995] revealed no evidence of carcinogenic activity when Sprague-Dawley rats (49-51 females/group; aged 7 weeks) were exposed to TCE (purity 99.8%; 0.13% carbon tetrachloride, 0.02% benzene and 0.019% epichlorohydrin) at 0, 50, 150 or 450 ppm (0, 270, 810 or 2430 mg/m^3) in air, 7 hours/day, 5 days/week for 104 weeks. At 100 weeks, about 50% of controls were alive compared with about 75% of the rats in the treated groups (Fukuda et al. 1983).

There was also no evidence of carcinogenic activity in a limited study where Wistar rats (30/sex/group; age unspecified) inhaled TCE (purity > 99.9%; 0.0015% triethanolamine; epoxide-free) at 0, 100 or 500 ppm (0, 540 or 2700 mg/m^3) in air, 6 hours/day, 5 days/week for 18 months, with study termination after 36 months. No differences in survival were reported (47, 23 and 37% of males, and 17, 13 and 17% of females in the control, low- and high-dose groups respectively. Histopathological and gross examination was carried out for the spleen, liver, kidneys, lungs, heart, stomach, central nervous system and “all tumours” (Henschler et al. 1980).

4.3.6 Inhalation studies – Hamster

Survival was unaffected and histopathological examination of spleen, liver, kidneys, lungs, heart, stomach, central nervous system and "all tumours" revealed no evidence of carcinogenic activity when Syrian hamsters (30/sex/group; age unspecified) were exposed to TCE (purity > 99.9%; 0.0015% triethanolamine; epoxide-free) at 0, 100 or 500 ppm (0, 540 or 2700 mg/m^3) in air, 6 hours/day, 5 days/week for 18 months, with study termination at 30 months (Henschler et al. 1980).

4.3.7 Dermal studies – Mouse

In a very limited study, 1 mg TCE was applied to the skin of 30 female ICR:Ha Swiss mice (6-8 weeks old), three times/week for 83 weeks. No tumours were observed at the application site (Van Duuren et al. 1979).

4.4 Laboratory animal cancer data (1995-2009)

No post-1995 cancer bioassays on TCE alone were identified. However, one report described a study investigating the ability of a mixture of chlorinated alkanes/alkenes, including TCE, to induce chronic toxicity and cancer in mice. The study involved the administration of the mixture to ICR mice (33-43/sex/group; age: described as weanling) in the drinking water at TCE concentrations of 0, 44, 106 or 471 mg/L for up to 18 months[4]. In males, the study was stopped at 16 months because survival in all groups had fallen to 53-57%. Survival was 61-76% in females at 18 months. Routine microscopic assessment was undertaken for the liver, kidneys, lungs, heart, testes, ovaries, uterus, vagina, oesophagus, stomach, small and large intestines and caecum. The males were said to show a general trend of a higher incidence of hepatocellular neoplasms (1/23, 3/18, 4/15 and 1/23 in control, low-, mid- and high-dose groups, respectively; $p < 0.05$ for the mid-dose). Adenoma and carcinoma were mentioned, but individual incidences were not specified. There was no biochemical evidence of liver damage, but liver weight was increased by 10% at the highest dose level (a dose level that did not increase tumour incidence). In the females, there was a significant ($p < 0.05$) increase in mammary gland adenocarcinomas at the high-dose (0/24, 1/28, 0/23 and 5/26 in the control, low-, mid- and high-dose groups, respectively). The investigators concluded that the mixture produced a promotional effect, increasing the incidences of lesions that are common in ageing mice (Wang et al. 2002).

[4] The approximate concentrations of the other compounds were, in mg/L, in the low-, mid- and high-dose groups: tetrachloroethylene (36, 90 and 607), 1,1-dichloroethane (6, 13 and 41), 1,1-dichloroethylene (1, 4 and 11), 1,1,1-trichoroethylene (2, 3 and 12), and chloroform (6, 8 and 14).

4.5 Modes-of-action for TCE tumours in laboratory animals – an overview

4.5.1 General comments

Although MOA considerations are not a key focus of this report, it was agreed that a brief overview of the recent understanding of mechanisms, as proposed by Expert Groups, could be helpful in regard to determining whether the results of rodent bioassays are predictive of a carcinogenic hazard to humans. In order to determine the relevance to humans of the tumours seen in laboratory rodent models, it is necessary to understand the mechanisms by which the rodent tumours developed, and whether the same mechanisms could operate in humans.

A detailed discussion on these aspects was not a key focus of this review, and this section is drafted (without further updating) primarily on the basis of the EU RAR that was published in 2004. The last comprehensive literature search for that EU report was carried out in 1995 but targeted searches were carried out thereafter, possibly up to 2001 when the member State Technical Experts finalised their review of the report. However, the latest date of the literature covered in regard to mechanism is not entirely clear (ECB, 2004).

The EU RAR on TCE was most concerned about mutagenicity and carcinogenicity, on the basis that it is not possible to identify a threshold exposure level below which these effects would not be expressed and therefore there are concerns for human health at all exposures. For workers, the RAR also expressed concerns over kidney toxicity (after repeated dosing), CNS depression (following acute exposure) and functional CNS disturbance (following repeated exposure) (ECB, 2004).

4.5.2 TCE, rodent tumours and Mode-of-Action

4.5.2.1 Introduction

Varying amounts of study data are available relating to an understanding of the mechanisms and the modes of action (MOAs) involved in development of the different tumours seen in rodents exposed to TCE (mouse liver and lung, and rat kidney). Certain key information is summarised below, and further details can be obtained from various Expert Group reports (e.g. ECB, 2004; HC, 2005; IARC, 1995; NRC, 2006; WHO, 2008).

4.5.2.2 MOA discussion for mouse liver tumours

Hepatocellular tumours have been induced in Swiss and B6C3F1 mice exposed to TCE by the inhalation and oral routes, but not in NMRI or Ha:ICR mice or any strain of rat tested so far. Syrian hamsters also did not develop liver tumours following inhalation exposure to TCE in the one study in which this species was tested. There is strong evidence linking the TCE metabolite trichloroacetic acid (TCA) and possibly also dichloroacetic acid (DCA) with the tumorigenic activity of TCE in certain strains of mice. Both metabolites are carcinogenic in mice but not in

rats. TCA was carcinogenic to male B6C3F1 mice treated by gavage at 150, 300 or 1000 mg/kg bw/day for up to 61 weeks (Bull et al. 1990; Herren-Freund et al. 1987). A limited study in female B6C3F1 mice given around 300 mg/kg bw/day over 52 weeks found no tumours, although the non-neoplastic pathology of the liver (accumulation of lipofuscin) was similar for both sexes. No tumours and no evidence of lipofuscin accumulation were found in a small study in a group of 3 male and 2 female Sprague-Dawley rats given around 300 mg/kg bw/day TCA in drinking water for 52 weeks (Bull et al. 1990). In a separate study, liver toxicity (not described further) was seen, but no tumours were observed, in male F344 rats (group size not stated) given up to 378 mg/kg bw/day TCA via drinking water for 2 years (DeAngelo and Daniel, 1992).

DCA was also carcinogenic in B6C3F1 mice but not Sprague-Dawley or F344 rats. The male mice given DCA orally for 52 weeks had a clear increase in liver tumours at around 300 mg/kg bw/day and a slight increase at 150 mg/kg bw/day. No tumours were found in a limited study in 10 female mice given 300 mg/kg bw/day, but an increase in the incidence of microscopic hyperplastic nodules suggested that longer exposure could have led to liver tumours (Bull et al. 1990; DeAngelo and Daniel, 1992). Liver tumours were also observed in a group of 33 male B6C3F1 mice treated with around 90 mg/kg bw/day DCA for 104 weeks (Daniel et al. 1992). No tumours were seen in a very limited study where 3 male and 2 female Sprague-Dawley rats were given around 300 mg/kg bw/day DCA in drinking water for 52 weeks. Non-neoplastic changes in these rats were very much less marked than those seen in mice at an equivalent dose. A more extensive study using male F344 rats (numbers not reported) found no evidence of liver tumours at doses up to 295 mg/kg bw/day for 60 weeks or 48 mg/kg bw/day for around 104 weeks. The top dose group was terminated early due to excessive treatment-related mortality (Bull et al. 1990).

In a comparison of TCA and DCA blood levels following TCA, DCA or TCE exposure, peak blood levels and areas under the curve for TCA in male B6C3F1 mice were similar following oral administration of either 20 mg/kg bw TCA or 200 mg/kg bw TCE. Following administration of a higher TCE dose (2000 mg/kg bw), peak blood levels of TCA were similar to those found after a dose of 100 mg/kg bw TCA but the area under the TCA blood concentration versus time curve was 2-fold greater after TCE. This suggests that, in mice, blood levels of TCA and DCA can reach potentially tumorigenic levels from TCE dose levels known to cause tumours. Similarly, peak DCA blood levels seen after an oral TCE dose of 2000 mg/kg bw were almost twice those seen after an oral DCA dose of 100 mg/kg bw (Bull et al. 1993; Larson and Bull, 1992a, 1992b).

In contrast to these findings, peak TCA blood levels were nearly 3-fold higher, and the area under the curve nearly 1.5-fold higher, in male Sprague-Dawley rats following a 20 mg/kg bw dose of TCA than after a 2000 mg/kg bw TCE dose. With higher TCA (100 mg/kg bw) and TCE (3000 mg/kg bw) doses, peak blood levels were still 3 times higher following the TCA dose, although the areas under the curve were the same. A much more striking difference was noted for DCA. DCA blood levels were below the limit of detection (0.5 μg/ml) following oral administration of 3000 mg/kg bw TCE to rats. When rats and mice were given an equivalent DCA dose, DCA blood levels were nearly twenty times higher in the rats. This indicates that not only do mice generate greater amounts of these metabolites compared to rats following TCE exposure, but also – based on the blood levels of TCA and DCA found in rats after exposure to

TCA and DCA respectively – that species differences also exist in sensitivity to the carcinogenic properties of these metabolites (Bull et al. 1993; Larson and Bull, 1992a, 1992b).

A number of studies have attempted to characterise the role of TCA and DCA in TCE-induced liver cancer. Ultrastructural examination showed that TCE induced peroxisome proliferation in male B6C3F1 and Alderley Park (Swiss) mice but not in male Osborne-Mendel or Alderley Park (Wistar derived) rats when given at 500-1500 mg/kg bw/day for 10 days by gavage in corn oil (Elcombe et al. 1985). Biochemical changes indicative of peroxisome proliferation were seen in B6C3F1 mice but not F344 rats given TCE at 500-2000 mg/kg bw/day for 10 days by gavage (Goldsworthy and Popp, 1987; Knuckles, 1990). In contrast, oral administration of TCA at 10-900 mg/kg bw/day to male Alderley Park and B6C3F1 mice and male Alderley Park and F344 rats for 10 days produced similar levels of peroxisome proliferation, as assessed by biochemical markers, in both species (Elcombe, 1985; Goldsworthy and Popp, 1987; Knuckles, 1990; Watson et al. 1993).

Biochemical evidence of peroxisome proliferation was apparently seen in Sprague- Dawley rats treated orally with TCA at around 350 mg/kg bw/day for 90 days (Mather et al. 1990). When TCA was given (in drinking-water for 2 weeks) at 330-720 mg/kg bw/day to male Osborne-Mendel and F344 rats, and at about 260-440 mg/kg bw/day to male Swiss-Webster, B6C3F1, C57BL/6 and C3H mice, there were relatively small increases in palmitoyl-Co A oxidase activity in the rat strains (238 and 163% increases for Osborne-Mendel and F344 rats respectively), whereas the increases were marked in all strains of mice (around 750% in Swiss-Webster, B6C3F1 and C3H mice, and 2000% in the C57BL/6 strain) (DeAngelo et al. 1989).

In rats, TCE metabolism to TCA is saturated at much lower dose levels than in mice (Prout et al. 1985). This difference in metabolism of TCE to a metabolite capable of inducing peroxisome proliferation probably accounts for the observed species difference in peroxisome proliferation in response to TCE. However, it does not explain why TCA-treated rats experience peroxisome proliferation but do not subsequently develop liver tumours (ECB, 2004).

Other effects that may play a role in the development of liver cancer and that have been investigated in rats and mice include hepatic DNA synthesis and mitosis. One study found similar increases in liver DNA synthesis in B6C3F1 mice given 2400 mg/kg bw/day TCE orally (222 and 181% after 3 and 21 days of exposure) and in Osborne-Mendel rats given 1100 mg/kg bw/day (121 and 175% after 3 and 21 days of dosing (Stott et al. 1982). In contrast, others observed much greater differences between rats and mice in TCE-induced liver DNA synthesis. When male Alderley Park and B6C3F1 mice and male Alderley Park and Osborne-Mendel rats were given 500-1500 mg/kg bw TCE for 10 days by gavage in corn oil, hepatic hypertrophy was observed in both species but only mice showed marked increases in DNA synthesis. At the top dose level, DNA synthesis was increased 478 and 574% in B6C3F1 and Alderley Park mice, respectively, whereas in rats, the maximum increases were 118 and 206% in the Osborne-Mendel and Alderley Park strains, respectively, and there was no dose-response relationship in either rat strain. Species differences in cell division in response to TCE were also reported. In both mouse strains, the incidence of mitotic figures was clearly increased whereas in rats TCE actually reduced the incidence of mitotic figures. Control rats had a 10-fold higher incidence of mitotic figures than control mice. There was no dose-relationship within treated groups for either species (Elcome et al. 1985). DNA synthesis was increased in B6C3F1 mice of both sexes given

100, 250, 500 or 1000 mg/kg bw/day TCE by gavage in corn oil. DNA synthesis increased with dose up to 250 mg/kg bw/day and then plateaued at approximately twice control levels (Dees and Travis, 1993). Increases in hepatocyte cell proliferation occurred in B6C3F1 mice of both sexes following gavage of 50, 200 or 1000 mg/kg bw TCE in corn oil. There was no induction of unscheduled DNA synthesis (Mirsalis et al. 1985). Rats were not tested in either study. It seems, then, that rats and mice may differ in TCE-induced increases in DNA synthesis and cell division (Stott et al. 1982; Elcombe et al. 1985; Dees and Travis, 1993; Mirsalis et al. 1985), although the data on TCE-induced DNA synthesis in Osborne-Mendel rats is inconsistent (Elcombe et al. 1985; Stott et al. 1982).

There are also some differences in the extent to which TCA affects liver DNA synthesis in rats and mice. When TCA was given in the drinking water, at about 900 mg/kg bw/day to male B6C3F1 mice and around 600 mg/kg/day to male F344 rats, for 7 days, the mice had a four-fold increase in cell proliferation whereas in rats cell proliferation dropped by 90% (Watson et al. 1993). When male B6C3F1 mice were given lower TCA doses (50-370 mg/kg bw/day) in drinking water for up to 15 days, no increase in cell replication was found but DNA synthesis was elevated after 5 and 14 days of treatment (Sanchez and Bull, 1990).

Both TCE (with metabolic activation) and TCA (without activation) inhibited gap junction mediated communication in mouse hepatocytes *in vitro* but not in rat hepatocytes (Klaunig et al. 1989). Chloral hydrate and trichloroethanol had no effect in hepatocytes of either species. The extent to which this finding may contribute to the development of liver tumours in mice, and the significance of this finding for human health is unclear (ECB, 2004).

It has been postulated that differences in the extent to which rats and mice metabolise TCE explain in part the species differences in toxicity; mice may generate sufficient TCA to exceed a threshold for peroxisome proliferation, whereas rats do not. The peroxisome proliferation is accompanied by sustained cell proliferation in mice, which can be expected to contribute to the eventual development of tumours (ECB, 2004).

DCA has not been investigated as extensively as has TCA but evidence suggests that the two metabolites may act by different mechanisms. DCA can induce peroxisome proliferation in B6C3F1 mice (and to a much lesser degree in Sprague-Dawley rats) but only at dose levels much higher than those shown to induce liver cancers in mice (Daniel et al. 1992; DeAngelo et al. 1989). Unlike TCA, DCA caused severe cytomegaly, glycogen accumulation, recurrent necrosis and regeneration of the liver when given to male B6C3F1 mice at 1 or 2 g/L in drinking water for 1 year (Bull et al. 1990). In a limited study in Sprague-Dawley rats given DCA at 5 g/L in water for 12 months, hepatocyte enlargement and glycogen accumulation were much less marked. Also, DCA can induce both cell division and DNA synthesis in male B6C3F1 mice (Sanchez and Bull, 1990).

Mice given tumorigenic doses of TCE produce blood levels of DCA equivalent to those seen after tumorigenic DCA doses, but the information on the extent of TCE metabolism to DCA in rats is conflicting. While some workers found that mice metabolise TCE to DCA to a much greater extent than do rats (Larson and Bull, 1992a), others reported that mice and rats produce similar amounts of DCA (Dekant et al. 1984; Green and Prout, 1985). However, the limited data

that are available suggest that mice are more sensitive to DCA than are rats, so DCA may also play a role in the development of TCE-induced liver tumours in mice (ECB, 2004).

For other TCE metabolites, no information was found on the carcinogenicity of trichloroethanol. Monochloroacetic acid (MCA) did not cause peroxisome proliferation in male B6C3F1 mice and male Sprague-Dawley rats given up to 482 and 501 mg/kg bw/day respectively in drinking water for 14 days (DeAngelo et al. 1989), or liver tumours in male F344 rats given 69 mg/kg bw/day in drinking water for 100-104 weeks (DeAngelo and Daniel, 1992). Chloral hydrate was carcinogenic when given to male B6C3F1 mice, either for 2 years (Daniel et al. 1992) or apparently even following a single dose (Rijhsinghani et al. 1986). No further details were provided from this study and no data on the carcinogenic potential of this metabolite in rats were available. The scarcity of data for other TCE metabolites means that it is not possible to draw conclusions about their possible role in tumour induction following TCE exposure.

Human hepatocytes do not undergo peroxisome proliferation in response to TCA. Whereas clear increases in peroxisome-specific β-oxidation activity were seen when hepatocytes from male Alderley Park rats and mice were exposed to various TCA concentrations *in vitro* for 3 days, no increase was seen in human hepatocytes. Furthermore, *in vitro*, the rate of metabolism of TCE to TCA in human hepatocytes was 3-fold and 120-fold more slowly than in rat and mouse hepatocytes, respectively (Elcombe et al. 1985). Other investigators have apparently found similar results (Knadle et al. 1990).

Less is known about the extent to which humans metabolise TCE to DCA (though it is likely to be a minor pathway), or about the effects of DCA in human liver, thus precluding any conclusions about the likely effects of metabolism of TCE to DCA in humans (ECB, 2004).

4.5.2.3 MOA discussion for mouse lung tumours

The TCE-induced mouse lung tumours may also have a metabolic basis. When male B6C3F1 mice, CD-1 mice of both sexes, and female Alderley Park rats were given single or repeated TCE doses by inhalation or intraperitoneal injection, lung toxicity was seen in mice but not rats (Forkert and Birch, 1989; Forkert et al. 1985; Green et al. 1997; Odum et al. 1992; Villaschi et al. 1991). Toxicity was only seen in one specific cell type, the Clara cell, a cell type known to be active in the metabolism of xenobiotics (though other lung cell types possessing xenobiotic metabolic activity were unaffected). There is also some evidence for strain and sex specificity for TCE-induced lung tumours, in that female Ha:ICR mice, male Swiss mice and B6C3F1 mice of both sexes seem to be sensitive whereas no female Swiss mice or NMRI mice of either sex are not (ECB, 2004).

Metabolic studies in Clara cells taken from female CD-1 mice showed that the major TCE metabolite in these cells was chloral hydrate and that the cells were relatively inefficient at metabolising it further. A single inhalation exposure of female CD-1 mice to 100 ppm chloral hydrate for 6 hours produced lung toxicity similar to that from TCE exposure. In contrast, no lung toxicity was seen following a single exposure to 100 ppm trichloroethanol for 6 hours, 500 ppm trichloroethanol for 2 hours or a single intraperitoneal dose of 200 or 500 mg/kg bw TCA

(Odum et al. 1992). It is thought that chloral hydrate accumulation in the Clara cell leads to cytotoxicity, leading to regeneration and replication to repair and replace the damaged Clara cells (Villaschi et al. 1991), resulting in repeated cycles of damage and regeneration that may lead eventually to lung tumour formation. Though chloral hydrate has given some evidence of mutagenic and clastogenic potential, negative findings from *in vivo* micronucleus and bone marrow cytogenetics studies in the rat using highly purified (purity 99.4%) chloral hydrate (Leuschner and Leuschner, 1991) reduce concerns that the initial step in mouse lung tumour formation may be a genotoxic event, and suggest that there may be other factors involved in the development of lung tumours in mice. There is also some evidence that chloral hydrate has carcinogenic activity. In one report an increase in liver tumours but not lung tumours was seen in male B6C3F1 mice given 166 mg/kg bw/day chloral hydrate in drinking water for 60 or 104 weeks (Daniel et al. 1992).

Liver tumours have also apparently been generated in male B6C3F1 mice following a single exposure to chloral hydrate but no further details of this study were available (Rijhsinghani et al. 1986). The lack of lung tumour formation following oral exposure to chloral hydrate and TCE can be explained if metabolism of TCE to chloral hydrate by Clara cells is a necessary step in the development of tumours in the mouse lung. When mice are exposed to TCE by the inhalation route, the Clara cells are directly exposed to TCE and consequently able to metabolically activate TCE to chloral hydrate. However, when mice are given TCE or chloral hydrate orally, these substances undergo metabolism before they reach the lungs and hence the Clara cell is not exposed to a xenobiotic that it cannot effectively detoxify (ECB, 2004).

TCE metabolism has also been studied in isolated rat and guinea pig lungs perfused with whole blood (Dalbey and Bingham, 1978) and exposed to TCE in the supplied ventilation gas. In both species trichloroethanol and TCA were detected in the perfusate, but not chloral hydrate and trichloroethanol-glucuronide. Levels of trichloroethanol in the perfusate increased with time and guinea pig lungs consistently produced more trichloroethanol than did rat lungs. Addition of ethanol to the perfusion blood did not affect the rate or extent of trichloroethanol formation. These data suggest that rat and guinea pig lungs may be able to metabolise TCE further than mouse lung, which may in part explain why rats did not develop lung tumours in long-term studies (ECB, 2004).

In *in vitro* studies using microsome preparations from mouse, rat and human lung tissue, metabolism of TCE to chloral hydrate was 23-fold greater in mouse than in rat preparations, and no conversion was detected in human microsomes. Conversion of chloral hydrate to trichloroethanol was similar for rat, mouse and human. Immunolocalisation of cytochrome P450IIE1, an isoenzyme involved in oxidative TCE metabolism, showed high concentrations in the Clara cells of the mouse, lower levels in the rat, and none in human lung sections. The study suggests major species differences in the pulmonary metabolism of TCE to chloral hydrate, with humans having an extremely low capability. No species differences in the capacity to metabolise chloral to trichloroethanol were apparent (Green et al. 1997).

4.5.2.4 MOA discussion for rat kidney tumours

In long-term studies, exposure to TCE by either the oral or inhalation route induced low incidences of renal adenoma and adenocarcinoma in a number of rat strains, but not in mice (Maltoni et al. 1988; NTP, 1988, 1990). Rats given TCE orally or by inhalation also develop non-neoplastic kidney lesions at relatively low dose levels. There is evidence that TCE produces species-specific toxicity in the kidneys of rats although there is some uncertainty surrounding the mechanism by which rat kidney lesions arise.

It has been suggested that the kidney tumours in rats arise as a result of persistent cytotoxicity and regeneration.

The available evidence suggests that one classic mechanism of kidney toxicity in male rats, involving hyaline droplet accumulation, is unlikely to be relevant to TCE-induced kidney lesions in male rats. Hyaline droplet (α2μ-globulin) accumulation and kidney cell replication in F344 rats of both sexes were unaffected by gavage dosing with TCE at 1000 mg/kg bw/day in corn oil for 10 days (Goldsworthy and Popp, 1987; Goldsworthy et al. 1988). Similar results were found when male F344 rats were given TCE at 2000 mg/kg bw/day in corn oil for 42 days (Green et al. 1990).

One mechanism by which TCE could cause cytotoxicity involves the formation of dichlorovinyl cysteine (DCVC) from TCE via a reductive glutathione conjugation pathway. Liver microsomes from Wistar rats can, in the presence of glutathione, transform TCE to S-(1,2-dichlorovinyl)glutathione and very low levels of this metabolite (0.3 μg/ml) have been detected by mass spectrometry in bile taken from male Wistar rats given a single gavage TCE dose of 2200 mg/kg bw in corn oil (Dekant et al. 1990). However, Ellis et al. (1995) using radiolabelled TCE or radiolabelled glutathione failed to detect glutathione conjugation in liver fractions from male F344 rats or humans. The limits of detection in their studies were 1 or 0.5 pmol/minute/mg protein respectively. It would be expected that if glutathione conjugation of TCE was occurring, this should also result in the excretion of the mercapturic acid N-acetyl DCVC in the urine. This metabolite has been isolated from the urine of rats, mice and humans (ECB, 2004).

In male Wistar rats around 0.8 μg in total of two stereoisomers of N-acetyl DCVC were isolated from urine collected over 24 hours following a gavage TCE dose of 2200 mg/kg bw in corn oil (Dekant et al. 1990). Birner et al. (1993) isolated between 1-4 μg/mL urine from male and female Wistar rats and NMRI mice given 50 mg/kg bw TCE orally and between 0.7-1 μg/mL urine from a group of four TCE workers (exposure levels were not reported). Birner et al. (1993) also compared urinary N-acetyl DCVC levels with urinary TCA levels in humans, rats and mice and found that human urine contained a much greater proportion of N-acetyl DCVC than urine from either rodent species, suggesting that humans may metabolise a greater proportion of TCE by this pathway. In male F344 rats given 500 or 2000 mg/kg bw TCE in corn oil for 1 or 10 days, N-acetyl DCVC was detected at very low levels, around 2-30 μg per 24-hour urine sample, accounting for only 0.001-0.008% of the dose (Green et al. 1990). N-acetyl DCVC has also been isolated from urine collected from male Sprague-Dawley rats given a single gavage dose of 400 mg/kg bw 1,2-^{14}C-TCE, accounting for less than 0.1% of the radioactivity dose (Dekant et al. 1986). It therefore seems likely that a low level of glutathione conjugation occurs *in vivo* and

consequently it would be expected that a low level of the metabolite DCVC is being generated (ECB, 2004).

It has been suggested that, in rats, the DCVC metabolite is activated locally in the kidneys by the enzyme β-lyase, and it is the case that in rats, TCE is specifically nephrotoxic to kidney tubules, where β-lyase is located in the tubular epithelium. Comparing the rate of activation of DCVC by the β-lyase pathway and the rate of deactivation by the N-acetyl transferase pathway *in vitro* in kidney cytosolic fractions from male F344 rats, male B6C3F1 mice and commercially available male human kidney cytosol, rats had the greatest capacity for metabolic activation via the β-lyase pathway (10-fold greater than that in mice or humans) but rats also had the highest capacity for metabolic deactivation by the N-acetyl transferase pathway (1.4-fold greater than mice and 60-fold greater than humans). Furthermore in rats, mice and humans metabolic clearance via the N-acetyl transferase pathway was substantially greater than activation by the β-lyase pathway (2 orders of magnitude greater in both rodent species and 27-fold greater in humans) (Ellis et al. 1995). Therefore there is some evidence that male rats have a greater capacity than mice to activate DCVC. However, since glutathione conjugation of TCE is a minor metabolic pathway and rats have a much greater capacity for metabolic deactivation than activation of DCVC, the amounts of active DCVC-based metabolites generated in rats *in vivo* are likely to be extremely low (ECB, 2004).

There is also evidence that N-acetyl DCVC can be deacetylated to regenerate DCVC. In kidney cytosolic fractions from F344 and Wistar rats, NMRI mice and humans (sexes not reported), mice were the most efficient deacetylators, followed by F344 rats. Human kidney cytosol and that from Wistar rats showed equivalent activity of just under one half that seen in mice and two-thirds that of F344 rats (Birner et al. 1993). Thus, even if N-acetyl DCVC were being reabsorbed from the kidney tubules (and so far there is no evidence of this), there seem to be no marked species differences that could explain the species differences in kidney toxicity (ECB, 2004).

To investigate the dose-dependency of urinary markers of metabolism via the glutathione pathway (markers were two isomers of N-acetyl DCVC) and the oxidative metabolic pathway (trichloroethanol + TCA as markers), four rats and three volunteers inhaled TCE at 40, 80 or 160 ppm for 6 hours. In both species, there were dose-related increases in the excretion of all markers, and the amount of oxidative metabolites excreted was three orders of magnitude higher than that of glutathione metabolites (Bernauer et al. 1996). Thus, the reductive metabolic pathway operated, but is quantitatively minor compared with the oxidative pathway, in humans and rats (ECB, 2004).

To investigate the possible role of glutathione conjugation in TCE-induced kidney toxicity in rats, the urine of Fischer 344 rats given TCE at 500 or 2000 mg/kg bw/day was analysed for N-acetyl DCVC and TCA on days 1, 5 and 10. N-acetyl DCVC excretion was at least 3 orders of magnitude lower than that of TCA, and accounted for between 0.001-0.008% of TCE dose. The relative sensitivity of rats and mice to DCVC-induced liver and kidney toxicity was determined by oral DCVC treatment at 1 or 50 mg/kg bw (single dose) or 0.1-5 mg/kg bw/day for 10 days. Mice were 5-10 fold more sensitive than rats to DCVC kidney toxicity. *In vitro* studies showed that the rate of TCE conjugation with glutathione in liver is slightly higher in mice (2.5 pmol/minute/mg protein) than in rats (1.6 pmol/minute/mg protein), and lower in humans (0.02-0.37 pmol/min/mg protein). *In vitro* comparisons of DCVC metabolism by renal β-lyase and

N-acetyl transferase indicated that metabolism by N-acetyl transferase was two orders of magnitude greater than by β-lyase in rats and mice, and 27-fold greater in humans; additionally, metabolic clearance via β-lyase activity in rats was 10-fold greater in the rat kidney than in the human and mouse kidney (Green et al. 1997). Again, these results do not satisfactorily explain the species differences in susceptibility to kidney toxicity. If TCE-induced kidney toxicity is related to the formation of DCVC and activation by β-lyase, then these findings would suggest that mice should be more sensitive than rats to TCE-induced kidney toxicity and carcinogenicity (ECB, 2004).

TCE metabolism by the reductive (glutathione) pathway was studied in 21 volunteers who inhaled 50 or 100 ppm TCE for 4 hours, with sampling of blood and urine before, during and after exposure for glutathione, related thiols and disulphides, and glutathione-derived (reductive) TCE metabolites. S-(1,2-dichlorovinyl)glutathione (DCVG) was found in the blood of all subjects from 30 minutes after the start of exposure. Peak blood concentrations and area under curve (AUC) for DCVG were greater in males. The distribution of values for both sexes was bimodal, suggestive of a polymorphism. DCVC was not detected in any volunteers. DCVC mercapturates were found in the urine of just one male volunteer (Lash et al. 1999). In a parallel study, the oxidative TCE metabolites were investigated in the same volunteers. AUCs for the oxidative metabolites were markedly higher than for DCVG, although peak levels were similar (TCA or trichloroethanol: 7-10 μg/ml; DCVG: 8-10 μg/ml) (Fisher et al. 1998). The study provides evidence that the glutathione (reductive) pathway operates in humans. The markedly higher AUCs for the oxidative metabolites and the absence of mercapturic acid conjugates in the urine of most volunteers support the view that the glutathione pathway is quantitatively minor for TCE. The failure to detect DCVC in the blood may be due to its unstable nature (ECB, 2004).

It has also been hypothesised that formic acid excretion may have a role in TCE-induced rat kidney toxicity and carcinogenesis (Green et al. 1998). When male Fisher rats (3-5/group) were exposed to TCE by gavage (1000 mg/kg bw/day) or inhalation (250 or 500 ppm, 6 hr/day), on a single occasion or for or up to 28 days, exceptionally high levels of formic acid were found in the urine of all TCE-exposed rats. Excretion peaked 2 days after a single exposure, or after 4 days of repeated exposure. After acute gavage with radiolabelled TCE, about 15% was excreted within 2 days, and about 86% of the urinary radioactivity was present as trichloroethanol glucuronide, suggesting that the formic acid was not a TCE metabolite (Green et al. 1998). Further experiments showed that the major metabolites of TCE, trichloroethanol and TCA, also stimulated folic acid excretion. Addition of folic acid to the diet or drinking water modulated the folic acid excretion response. Also, it was found that two markers of vitamin B12 deficiency, urinary methylmalonic acid and plasma 5-methyltetrahydrofolate, were increased following repeated oral exposure to trichloroethanol. The investigators postulated that TCA and trichloroethanol interact with vitamin B12, inducing a vitamin B12 deficiency, which causes inhibition of the B12-dependent methionine salvage pathway, and leads to folate deficiency. As a result of this folate deficiency, the metabolic pathway that utilises formic acid is disrupted and excess formic acid is excreted in the urine. There is little information on whether TCE influences the methionine salvage pathway or formic acid excretion in humans (Dow and Green, 2000).

4.5.2.5 Overview of MOA conclusions

4.5.2.5.1 Mouse liver

There is a growing body of evidence to show that development of liver tumours in mice exposed to TCE is linked to the way mice metabolise the substance. In mice, TCE is much more readily metabolised to TCA, a metabolite which can induce peroxisome proliferation and cell proliferation in this species. It is likely that these effects lead to the development of mouse liver tumours. Studies *in vitro* have shown that the extent to which TCE is metabolised to TCA in human hepatocytes is closer to that found in rat hepatocytes (i.e. much less than in mouse cells). Rats do not develop liver tumours following TCE exposure. In addition, human hepatocytes do not undergo peroxisome proliferation in response to TCA, unlike mouse and rat hepatocytes. It therefore seems reasonable to conclude that the effects of TCA in mice are unlikely to be of relevance for humans. The role of the minor metabolite DCA has been less extensively investigated but, from currently available evidence, it seems that the effects of this metabolite may also be mouse-specific. Experts have concluded that, overall, although TCE can induce liver tumours in mice, the weight of evidence available indicates that this finding is unlikely to be of significance for human health (e.g. ECB, 2004).

4.5.2.5.2 Mouse lung

There is evidence linking the development of TCE-induced mouse lung tumours with its metabolism to chloral hydrate in the Clara lung cells. It has been shown *in vitro* that mouse Clara cells will metabolise TCE to chloral hydrate but are inefficient at detoxifying this metabolite, leading to the build-up of chloral hydrate within the Clara cell and presumably resulting in cytotoxicity and repeated cycles of cell destruction and replication, ultimately leading to tumour formation. Lung tumours were not seen in TCE-exposed rats. Perfused rat lungs exposed to TCE *in vitro* did not accumulate chloral hydrate, and human lung tissue appears to possess a negligible capability to metabolise TCE to chloral hydrate. This suggests that the TCE-induced lung tumours seen in mice are not relevant to humans (e.g. ECB, 2004).

4.5.2.5.3 Rat kidney

The mode of action by which TCE-exposed rats develop kidney tumours is less clear. These tumours may arise as a secondary result of repeated cytotoxicity. Two biologically-plausible modes of action for TCE-induced kidney toxicity and tumour formation in rats have been proposed. The first involves metabolism via the glutathione conjugation pathway to form DCVC, which can be activated by renal β-lyase to reactive metabolites that are known to be mutagenic and nephrotoxic. Species differences in the rates of glutathione conjugation and activation of DCVC by β-lyase have been identified, but these differences are not consistent with the known species differences in sensitivity to kidney toxicity. The presence of metabolites from the glutathione pathway has been detected in humans. This is quantitatively a very minor pathway in all species, although this is not convincing evidence of a lack of toxicological significance. The

second proposed mode of action involves a TCE-induced increased excretion of formic acid, possibly resulting from an inhibition of the methionine salvage pathway. Whether this mode of action can operate in humans is not known. Thus there remains considerable uncertainty surrounding the modes of action by which TCE induces nephrotoxicity in rats, their relative importance to rat kidney tumour formation, the relevance to humans and, indeed, whether other uninvestigated modes of action have a role (ECB, 2004).

4.6 TCE and generation of tumours as a function of exposure route

In respect of TCE exposure, cancer target site and exposure route specificity, useful human data are restricted to the inhalation route and thus provide no real opportunity to assess any exposure-route specificities in target tissue for TCE and cancer.

Inhalation and oral route lifetime bioassays are available in both rats and mice, providing – at least in principle – an opportunity to study the possible existence of relationships between cancer target tissue and TCE exposure route. Rats showed no evidence of route specificity, developing low incidences of kidney tumours following either oral or inhalation exposure to TCE. Mice developed liver tumours following exposure by either of these two exposure routes. Lung tumours were seen in mice only following inhalation exposure. However, as TCE-induced mouse liver and lung tumours are probably not relevant to humans, these findings may not be especially helpful.

Data relevant to thedermal route are essentially absent.

5. DISCUSSION (INCLUDING SCOPE AND LIMITS OF RESULTS)

5.1 TCE carcinogenicity – overview of laboratory animal studies

The carcinogenicity of TCE has been investigated in a number of long-term laboratory animal studies, using the oral and inhalation routes, and involving various strains of rats and mice, as well as hamsters. These studies provided clear evidence that TCE is carcinogenic in rats and mice.

In two adequate oral studies in mice, TCE induced benign and malignant liver tumours. A possible increase in liver tumours was also seen in a more recent mouse study involving administration of a mixture of chlorinated alkanes/alkenes, including TCE, in the drinking water. Most of the seven oral TCE studies in rats were inconclusive (because treatment time was too short or survival was reduced), but two studies found increases in uncommon renal-cell tumours in males, and one study reported an increase in interstitial testicular tumours.

Increases in lung tumours were seen in three of the four mouse inhalation studies in mice, and liver tumours or lymphomas were increased in individual studies. In one of the three rat inhalation studies, the males showed an increase in interstitial testicular tumours and a marginal

increase in renal-cell tumours. No evidence of carcinogenic activity was seen in hamsters exposed to TCE by the inhalation route.

In limited studies involving topical application or subcutaneous injection, TCE or a proposed metabolite (TCE-oxide) did not increase skin tumour or local sarcoma incidence in mice.

The weight of evidence available has led Expert Groups to conclude that the mouse lung and mouse liver tumours induced by TCE are unlikely to be of significance for human health. However, the precise mechanisms by which TCE induces kidney tumours in rats have not been elucidated completely, and thus there remains considerable uncertainty regarding the relevance of this finding to TCE-exposed humans (ECB, 2004; HC, 2005; IARC, 1995; NRC, 2006; USEPA, 2009; WHO, 2008).

Tables 4 and 5 summarize the published TCE cancer studies in rats and mice. A summary is given in Table 6 and an overview (showing target tissues and exposure routes) is provided in Table 8.

5.2 TCE carcinogenicity – overview of epidemiology studies

Although there are numerous reports of health surveys carried out on workers occupationally exposed to TCE, their value is severely limited by the lack of any detailed information on the atmospheric TCE levels, exposure to other chemicals including alcohol consumption, and on other potential confounding factors. Furthermore, in many cases, no worker control group was used and comparisons were instead made with the general population. Consequently it is difficult to assess either the qualitative or quantitative relationship any observed health effects may have with historic TCE exposure.

The risk of developing cancer as a result of occupational exposure to TCE has been investigated in a number of cohort studies in which the mortality (and sometimes morbidity) of a group of exposed workers is compared with that of the general population. In this type of study, comparisons between the general population have been adjusted for age and gender, but not for other potentially confounding lifestyle variables such as alcohol consumption and smoking.

IARC concluded that the three most informative studies available at the assessment date (Anttila et al. 1995; Axelson et al. 1978, 1984, 1994; Spirtas et al. 1991) consistently indicated an excess relative risk for cancer of the liver and biliary tract, with a total of 23 observed cases and 12.87 expected. No increase in risk for these cancers was seen in the fourth, more limited cohort study (Garabrant et al. 1988). In two studies (Anttila et al. 1995; Spirtas et al. 1991), risks for liver cancer were reported separately, and these observed a total of 7 cases compared with 4.0 expected (IARC, 1995). The three most informative cohort studies (Anttila et al. 1995; Axelson et al. 1978, 1984, 1994; Spirtas et al. 1991) also were consistent in showing a modest increase in risk of non-Hodgkin's lymphoma, with a total of 27 cases and 18.9 expected. Again, no increase in risk was seen in the fourth cohort study (Garabrant et al. 1988). The elevated risks in liver and biliary tract cancer, and in non-Hodgkin's lymphoma, in all three of the most informative cohort studies were considered by IARC to be the most important observations. IARC also noted that

some of the available studies had reported increased risks in other cancers, including cervix, kidney, urinary bladder and leukaemia, but no clear conclusions were reached for these (IARC, 1995).

A more recent TCE evaluation was produced by the Institute for Health and Consumer Protection of the European Union Chemical Bureau (ECB, 2004). ECB concluded that the majority of studies of TCE-exposed workers did not show any evidence that TCE exposure is associated with an increased incidence of cancer. It was also mentioned that individually, each of the "negative" studies had certain limitations although several (Axelson et al. 1994; Blair et al. 1998; Boice et al. 1999; Morgan et al. 1998; Spirtas et al. 1991), by nature of their design, had substantial power to detect an effect, and when taken together provide significant evidence that TCE is not carcinogenic in humans under the exposure conditions experienced by the groups studied. It was pointed out that the occupational studies did not provide complete reassurance of the absence of TCE-related carcinogenicity in humans because there was limited evidence of an increased risk of cancer, in particular non-Hodgkin's lymphoma, among TCE-exposed workers in one well-conducted cohort study (Anttila et al. 1995). Furthermore, two other studies reported an increased risk of kidney cancer in groups of TCE workers (Henschler et al. 1995; Vamvakas et al. 1998), who had possibly experienced higher exposures than the workers in the previously-mentioned studies. It was suggested that the lack of corroboration between these two studies and the other epidemiology studies may be because of the differences in TCE exposure levels. However, it was not possible to draw firm conclusions from the Henschler et al. (1995) and Vamvakas et al. (1998) studies because of methodological weaknesses, but the reported associations add to the concerns about the carcinogenic potential of TCE (ECB, 2004).

An EU group of Specialised Experts subsequently concluded that several cohort investigations (Anttila et al. 1995; Axelson et al. 1994; Blair et al. 1998; Boice et al. 1999) show an association between exposure to TCE and development of non-Hodgkin's lymphoma, but bias and confounders could not be completely ruled out. With the exception of one, all of these Specialised Experts considered that the evidence did not meet the criteria for classification as an EU category 1 carcinogen[5]. One Expert, in support of category 1, underlined the evidence for kidney tumours in humans and the consistency with the S-(1,2-dichlorovinyl)-L-cysteine (DCVC) metabolic pathway and the observation of a different spectrum of somatic mutations in kidney tumours of TCE-exposed patients compared to unexposed patients. A clear majority of the Specialised Experts recommended that classification of TCE as a category 2 carcinogen[6] was warranted, based on evidence in one animal species, namely tumours in the rat kidney, supported by epidemiological data showing an association between exposure and kidney tumours and non-Hodgkin's lymphoma in humans. Some Specialised Experts stated that genotoxicity and metabolic/biochemical findings added to their concern. One expert maintained that category 1 was appropriate, and one preferred category 3 classification[7] but accepted the majority view. In

[5] Carcinogen Category 1: Substances known to be carcinogenic to humans.

[6] Carcinogen Category 2: Substances which should be regarded as if they are carcinogenic to humans. There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer, generally on the basis of: 1. appropriate long-term animal studies; 2. other relevant information.

[7] Carcinogen Category 3: Substances which cause concern for humans, owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment.

April 2000, the EC's Working Group on the Classification and Labelling of Dangerous Substances decided to accept the recommendation made by the Specialised Experts and it was agreed that the existing classification and labelling of TCE would need to be revised accordingly (ECB, 2004).

The EU evaluation hinged strongly on the apparent discrepancies between studies and highlighted that several of the "negative" studies (Axelson et al. 1994; Blair et al. 1998; Boice et al. 1999; Morgan et al. 1998; Spirtas et al. 1991) had sufficient power to detect associations between TCE exposure and cancer. A few comments are worth making:

- A negative study can only be considered to be truly negative if it is sufficiently informative (Ahlbom et al. 1990). With regard to the available evidence, it is clear that for many of the negative studies, exposure assessments had not always been conducted on the basis of actual exposure measurements. If measurements were available, numbers of measurements, spread over the risk period of the cohort, distribution over occupational categories and other aspects of documentation on the use of these measurements, are not made explicit in the published reports. Most negative studies are based on expert evaluations, sometimes in combination with measurements. This approach can be appropriate in many cases, but the accuracy has not been established. Thus, exposure misclassification cannot be excluded and, more importantly, the potential magnitude and direction of any exposure misclassification is not known. Although exceptions exist, the effect of non-differential misclassification is that it usually leads to underestimation of the exposure-response relationship (Armstrong, 1998).

- In addition to these comments regarding the exposure assessment, it should be noted that workers in several of the cohort studies were exposed to TCE and to other solvents. The crude categorization by TCE exposure is not sufficiently accurate to avoid potential confounding by other exposures. Adjustments for other exposure have generally not been made (Wartenberg et al. 2000a, 2000b).

- The power of some of the available studies seems considerable, especially those that accumulated a high number of person-years. However, the cancers that were seen as potentially associated with TCE exposure in the evaluation by IARC and which are of particular interest (non-Hodgkin's lymphoma, liver and biliary tract cancer, and kidney cancer) are relatively rare, and the power of most cohort studies is rather limited.

- Mortality studies might be difficult to compare with incidence studies, especially the more recent ones, because many cancers do not necessarily lead to increased mortality over a short time period. The mortality rates for different cancers are likely to differ and as a result, incidence studies are to be preferred. Clear evidence for a changing mortality rate for non-Hodgkin's lymphoma is presented by Wartenberg (2007).

These aspects limit the interpretation of the available evidence and make it difficult to consider some "negative" studies as informative negative studies. Compared to the earlier (IARC, 1995) evaluation the available evidence is increased only to a very limited extent. One well-designed study made use of TCA biomarker measurements (Hansen et al. 2001). This study found a positive association between TCE exposure and non-Hodgkin's lymphoma and thus adds some,

but limited, evidence. The same applies for another Danish study by Raaschou-Nielsen et al. (2003). Overall, the picture has hardly changed since the evaluation by IARC, when it is considered that some of the negative studies can not be considered as very informative. Findings from cohort studies with less accurate assessment of TCE exposure have been more variable. TCE exposure has been assessed less accurately in case-control studies. In most case-control studies TCE exposure was estimated from exposures to solvents in general. These studies typically reported higher cancer rates for tumour sites similar to those observed in the cohort studies.

A third evaluation has been published by the US National Toxicology Program (DHHS, 2005). This evaluation makes use of the literature review by Wartenberg et al. (2000a), which also contains a meta-analysis (a meta-analysis usually produces a quantitative summary of the association between TCE exposure and a specific cancer based on several studies using weighing techniques). The included evidence comes from seven cohort studies with specific TCE exposures well characterized for individual study subjects. A meta-analysis of these cohort studies found that occupational exposure to TCE was associated with excess incidences of liver cancer, kidney cancer, non-Hodgkin's lymphoma, prostate cancer and multiple myeloma, with the strongest evidence for the first three listed cancers. Elevated risks of death from Hodgkin's disease, multiple myeloma, cervical cancer, and liver cancer were also observed in this analysis (Wartenberg et al. 2000a).

It seems useful to consider in the light of this evaluation some of the recently published meta-analyses. Mandel et al. (2006) conducted a meta-analysis that included 14 occupational cohort and four case-control studies of workers exposed to TCE, to investigate the potential relationship between TCE exposure and the risk of non-Hodgkin's lymphoma (NHL). The summary relative risk estimates (SRRE) for the group of cohort studies that had what was considered more detailed information on TCE exposure was 1.29 (95% CI: 1.00-1.66) for the total cohort and 1.59 (95% CI: 1.21-2.08) for the seven studies that identified a specific TCE exposed sub-cohort. The authors concluded that interpretation of overall findings for cohort studies was hampered by variability in results across studies, such as limited exposure assessments, lack of evidence of exposure-response trends, lack of supportive information from toxicological and mechanistic data, and absence of consistent findings in epidemiologic studies of exposure and NHL. Although a modest positive association was found in the TCE sub-cohort analysis, a finding attributable to studies that included workers from multiple industries, there is insufficient evidence to suggest a causal link between TCE exposure and non-Hodgkin's lymphoma. A transparent evaluation of study design issues as proposed by Vlaanderen (2009) was not conducted. Unfortunately, analyses were not limited to studies with quantitative exposure information based on TCA biomarker monitoring. Similar comments were made by Wartenberg (2007) who criticised this meta-analysis because of the stratification strategy chosen: (1) the population source (multiple industries versus aerospace only); (2) the outcome measures considered (incidence versus mortality); and (3) location (European versus US). An analysis in which different aspects of study design such as type of exposure assessment would have been specified *a priori* would have given more insight into factors contributing to study outcomes than focusing on population source. A more prudent interpretation of the literature seems more justified, leading to the conclusion that increasing support is available for a causal relationship between TCE and non-Hodgkin's lymphoma.

The same group also published meta-analyses for multiple myeloma or leukaemia (Alexander et al. 2006) and liver tumors (Alexander et al. 2007), following the same methodology as used in the non-Hodgkin's lymphoma analysis. The same comments apply to these meta-analyses, especially the comment referring to the variables considered as potential determinants of study heterogeneity.

Recently, the US Environmental Protection Agency published a draft Toxicological Review of Trichloroethylene: in Support of Summary Information on the Integrated Risk Information System (IRIS) for public comment (USEPA, 2009). Meta-analyses have been included for kidney cancer, non-Hodgkin's lymphoma and liver cancer. For kidney cancer it was concluded that most cohort studies, including several negative studies, lacked the statistical power to detect a doubling of kidney cancer risk. A meta-analysis of 14 studies yielded a pooled Relative Risk (RRp) estimate of 1.25 (95% CI: 1.11-1.41). A risk analysis was conducted using the study by Charbotel et al. (2006) using a life table analysis. This study is considered as extremely informative and of high quality. This is one aspect of the analysis which can be debated since the number of cases with TCE exposure is low, other exposures are present and the exposure is characterized in the best possible way for this type of design, but still relatively crude compared to biomonitoring studies, as argued before. The authors of this paper acknowledge this and observed that exposure to TCE was strongly associated with exposure to cutting fluids and petroleum oils. About 90.3% of subjects exposed to cutting oils were also exposed to TCE, and 57.9% of those exposed to TCE were exposed to cutting oils. For other petroleum oils, 83.6% of subjects exposed to other oils were also exposed to TCE, and, conversely, 31.7% of those exposed to TCE were also exposed to other oils. When exposure to cutting fluids and to other petroleum oils were added to the conditional logistic regression model, the OR for renal cell carcinoma (RCC) in the highest class of cumulative TCE exposure was reduced to 1.96 (95% CI: 0.71-5.37). When considering the combined effect of cumulative and peak exposures, the OR for the high-exposure group with peaks was 2.63 (95% CI: 0.79-8.83), after adjusting for smoking, BMI and exposure to cutting fluids and other petroleum oils. In the USEPA draft document it was concluded that the finding of a higher kidney cancer risk for both cutting oil and TCE exposure >50 ppm, compared to cutting oil alone, supports a TCE effect for kidney cancer. Adjustment for cutting oil exposures, furthermore, did not greatly affect the magnitude of TCE effect measures in the many analyses presented by Charbotel et al. (2006, 2009) suggesting cutting fluid exposure as not greatly confounding TCE effect measures. There is an element of over-interpretation of this study given the low numbers of exposed individuals. However, the weight of this study in the meta-analysis of kidney cancer was small compared to some of the cohort studies (USEPA, 2009).

The meta-analysis for liver cancer for the highest exposure groups in six studies provided a Relative Risk estimate of 1.32 (95% CI: 0.93-1.86), similar to the RRp estimate for liver and gallbladder/biliary cancer and any TCE exposure of 1.33 (95% CI: 1.09-1.64). The estimate of the highest-exposure groups is dominated by the study by Raaschou-Nielsen et al. (2003) (USEPA, 2009).

Meta-analysis of the highest exposure groups for non-Hodgkin's lymphoma, either by duration, intensity, or their product, cumulative exposure, results in an RR of 1.57 (95% CI: 1.27-1.94),

which is greater than the RR found for the overall exposure analysis, and provides additional support for an association between NHL and TCE (USEPA, 2009).

The conclusion of the draft USEPA report is that "TCE is characterized as carcinogenic in humans by all routes of exposure. This conclusion is based on convincing evidence of a causal association between TCE exposure in humans and kidney cancer. The human evidence of carcinogenicity from epidemiologic studies of TCE exposure is compelling for non-Hodgkin's lymphoma but less convincing than for kidney cancer, and more limited for liver and biliary tract cancer" (USEPA, 2009).

Tables 1-3 summarize the key published cohort and case-control TCE cancer studies in humans. An overview is given in Table 7.

5.3 TCE exposure route and cancer target tissues

In respect of TCE exposure, cancer target site and exposure route specificity, useful human data are restricted essentially to the inhalation route and thus provide no real opportunity to assess any exposure-route specificities in target tissue for TCE and cancer. Occupational exposure may well have also involved a dermal component, but it is impossible to disentangle such a contribution from the inhalation exposure, the latter exposure route being likely to represent the most important contributor to total intake.

Inhalation and oral route lifetime bioassays are available in both rats and mice, providing an opportunity to study the possible existence of relationships between cancer target tissue and TCE exposure route. Rats showed no evidence of route specificity, developing low incidences of kidney tumours following either oral or inhalation exposure to TCE. Mice developed liver tumours following exposure by either of these two exposure routes, showing a lack of exposure route specificity for this tumour site. However, mice only developed lung tumours when exposed by inhalation, and not following ingestion. In any case, TCE-induced mouse liver and mouse lung tumours are probably not relevant to humans, and so these findings are not especially insightful in respect of route specificity.

Good quality data relating to cancer and dermal TCE exposure of laboratory animals is lacking, the database consisting solely of an inadequate test in mice.

Tables 7 and 8 provide overviews showing conclusions relating to TCE exposure and target tissues in humans and laboratory animals, respectively.

5.4 Effect of duration and latency period on cancer risk

The available information was too limited to allow any real insights into the minimum duration of exposure or latency period associated with an increased cancer risk. Where information was

available, the inclusion of a 20-year latency period in the analysis resulted in an increase in cancer risk.

6. CONCLUSION

6.1 TCE and cancer in laboratory animals

The carcinogenicity of TCE has been investigated in a number of long-term laboratory animal studies, using the oral and inhalation routes, and involving various strains of rats and mice, as well as hamsters. These studies provided clear evidence that TCE is carcinogenic in rats and mice. In two adequate oral studies in mice, TCE induced benign and malignant liver tumours. A possible increase in liver tumours was also seen in a more recent mouse study involving administration of a mixture of chlorinated alkanes/alkenes, including TCE, in the drinking water. Most of the seven oral TCE studies in rats were inconclusive (because treatment time was too short or survival was reduced), but two studies found increases in uncommon malignant renal-cell tumours in males, and one study reported an increase in interstitial testicular tumours. Increases in benign and malignant lung tumours were seen in three of the four mouse inhalation studies in mice, and maligant liver tumours or lymphomas were increased in individual studies. In one of the three rat inhalation studies, the males showed an increase in interstitial testicular tumours and a marginal increase in malignant renal-cell tumours. No evidence of carcinogenic activity was seen in hamsters exposed to TCE by the inhalation route. In limited studies involving topical application or subcutaneous injection, TCE or a proposed metabolite (TCE-oxide) did not increase skin tumour incidence in mice.

The weight of evidence available has led Expert Groups to conclude that the mouse lung and mouse liver tumours induced by TCE are unlikely to be of significance for human health. However, the precise mechanisms by which TCE induces kidney tumours in rats have not been elucidated completely, and thus there remains considerable uncertainty regarding the relevance of this finding to TCE-exposed humans (ECB, 2004; HC, 2005; IARC, 1995; NRC, 2006; WHO, 2008).

Inhalation TCE cancer studies in rats and mice are summarised in Table 4, and oral studies in Table 5. A summary of the rodent cancer data are given in Table 6. Table 8 provides an overview showing the relationships between exposure route and target tissues.

6.2 TCE and cancer in humans

There are numerous reports of health surveys carried out on workers occupationally exposed to TCE, but their value is, in general, severely limited by the lack of any detailed information on the atmospheric TCE levels, on exposure to other chemicals including alcohol consumption, and on other potential confounding factors. Furthermore, in many cases, no worker control group was used and comparisons were instead made with the general population. Consequently it is difficult to assess either the qualitative or quantitative relationship between any observed health effects

and past TCE exposure. The risk for developing cancer as a result of occupational exposure to TCE has been investigated in a number of cohort studies in which the mortality (and sometimes morbidity) of a group of exposed workers is compared with that of the general population. In this type of study, comparisons between the general population have been adjusted for age and gender, but not for other potentially confounding lifestyle variables such as alcohol consumption and smoking.

IARC concluded that the three most informative studies available at the time of assessment (1995) consistently indicated an excess relative risk for cancer of the liver and biliary tract, while no increase in risk for these cancers was seen in the fourth, more limited cohort study. The three most informative cohort studies were also consistent in showing a modest increase in risk of non-Hodgkin's lymphoma. Again, no increase in risk was seen in the fourth cohort study. The elevated risks in liver and biliary tract cancer, and in non-Hodgkin's lymphoma, in all three of the most informative cohort studies were considered by IARC to be the most important observations. IARC also noted that some of the available studies had reported increased risks in other cancers, including cervix, kidney, urinary bladder and leukaemia, but no clear conclusions were reached for these (IARC, 1995). More recently, ECB and USEPA experts have concluded that the epidemiological data supporting an association between TCE exposure and human cancer are strongest for kidney cancer and non-Hodgkin's lymphoma (ECB, 2004; USEPA, 2009).

Few newer studies add strong additional evidence since the IARC evaluation was published (IARC, 1995). One newer well-designed study that made use of TCA biomarker measurements (Hansen et al. 2001) found a positive association between TCE exposure and non-Hodgkin's lymphoma and thus adds some, but limited, evidence. The same applies for another Danish study (Raaschou-Nielsen et al. 2003). Overall, the picture has hardly changed since the evaluation by IARC, when it is considered that some of the negative studies cannot be considered as very informative. Findings from cohort studies with less accurate assessment of TCE exposure have been more variable. TCE exposure has been assessed less accurately in case-control studies. In most case-control studies TCE exposure was estimated from exposures to solvents in general. These studies typically reported higher cancer rates for tumour sites similar to those observed in the cohort studies.

If the evaluation is limited to studies with stronger, more reliable exposure assessment components (these are usually cohort studies), especially those with exposure quantified by using urinary TCA as a biomarker of TCE exposure, then epidemiological investigations do provide indications for carcinogenicity of TCE in humans. In these studies, the increase in risk of developing cancer as a result of occupational TCE exposure was not large, and the risk was generally less than doubled (relative risk less than 2) for any of the tissue sites that have been considered; excess risks may be largely associated with the presumably higher exposures in the more distant past. An association between occupational TCE exposure and cancer in humans was most consistently found for kidney cancer and non-Hodgkin's lymphoma, with more limited evidence for liver cancer. The studies in which elevated risks have been observed for these cancers generally involved workers with long-term, high exposure to TCE, sometimes throughout their entire working life.

TCE cancer epidemiology studies are summarised in Table 1 (those key to the IARC evaluation), Table 2 (more recent cohort studies) and Table 3 (more recent case-control studies). Table 7 provides an overview of the evidence for TCE exposure and target tissues.

6.3 TCE exposure route and cancer target tissues

In respect of TCE exposure, cancer target site and exposure route specificity, useful human data are restricted to the inhalation route and thus provide no real opportunity to assess any exposure-route specificities in target tissue for TCE and cancer. There was no convincing evidence of any increased risks of cancer in limited population studies where the residents had been exposed to low concentrations of TCE in the groundwater or drinking water, which would have resulted in mainly oral exposure and, to a lesser extent, dermal exposure. These studies offered only limited insights into TCE's cancer potential.

Inhalation and oral route lifetime bioassays are available in both rats and mice, providing an opportunity to study the possible existence of relationships between cancer target tissue and TCE exposure route. Rats showed no evidence of route specificity, developing low incidences of kidney tumours following either oral or inhalation exposure to TCE. Mice developed liver tumours following exposure by either of these two exposure routes. Lung tumours were seen in mice only following inhalation exposure. However, as TCE-induced mouse liver and mouse lung tumours are probably not relevant to humans, these findings offer no real insights into the possibility of exposure-route specific targets in TCE-exposed humans.

Table 8 provides an overview showing the relationships between exposure route and target tissues in laboratory rodents.

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APPENDIX

Bibra - toxicology advice & consulting

The TRACE database and databank

TRACE includes information from peer-reviewed toxicology and nutrition journals as well as secondary sources and websites. In addition to primary literature on the health effects of chemicals, TRACE covers official publications and evaluations issued by authoritative groups including:

- WHO/IPCS reports and evaluations (including CICADs and EHCs, and IARC, JECFA and JMPR monographs), and the WHO Air Quality and Drinking-Water Quality Guidelines
- OECD SIDS dossiers/SIARS
- IUCLID data sets
- EU Risk Assessment Reports
- EU expert committee opinions (including EU scientific committees, and EFSA scientific panels) and other reports from EU agencies and institutes etc (including ECHA, ECVAM, EMEA and CPS&Q)
- ECETOC, HERA, Council of Europe and other pan-European programmes
- UK government agency (including Defra, EA, FSA, DoH, HSE, HPA, PSD and VMD) and advisory committee (eg COT, COM, COC, ACNFP, SACN, ACP, ACAF, VPC, VRC and ACRE) reports and evaluations
- Opinions from other UK organisations such as the Royal Society
- US agency reports and evaluations (EPA, ATSDR, FDA, NTP, OSHA, NCEA, CFSAN, CERHR, NIEHS, CDC, OEHHA and ACGIH)
- Health Canada evaluations
- BUA, DFG, BG Chemie and BfR reports and monographs
- Gezondheidsraad opinions, including those from its various committees such as DECOS
- RIVM reports
- Danish EPA reviews
- Reports and other information provided by Swedish governmental organisations, including the National Food Administration and the Swedish Chemicals Agency
- Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals
- Australian agency reviews including NICNAS Priority Existing Chemical Assessments, APMVA reports and (jointly with New Zealand) FSANZ assessments
- Japanese Chemical Industry Ecology-Toxicology & Information Center reports
- CIR, RIFM and other specialist industry groups
- **bibra** Toxicity Profiles

Table 1. Summary of data from four cohort studies of trichloroethylene (taken from Table 11 [IARC, 1995])

Cancer site	Axelson et al. (1994) 1421 men using trichloro-ethylene and monitored for exposure (Sweden, 1958-87)			Anttila et al. (1995) 3089 men and women using trichloroethylene and monitored for exposure (Finland, 1967-92)			Spirtas et al. (1991) 7282 men and women employed in aircraft maintenance and exposed to trichloroethylene (USA, 1953-82)			Garabrant et al. (1988) 14 067 men and women employed in aircraft manufacture (USA,1958-82)		
	SIR	95% CI	Obs	SIR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs
All cancers	0.96	0.80-1.2	107	1.1	0.92-1.2	208	[0.88]	[0.78-0.99]	281	0.84	0.77-0.93	453
Oesophagus	NR			NR			[1.0]	[0.37-2.2]	6	1.1	0.62-1.9	14
Stomach	0.70	0.23-1.6	5	1.3	0.75-2.0	17	[0.78]	[0.43-1.3]	14	0.40	0.18-0.76	9
Colon	1.0	0.44-2.0	8	0.84	0.36-1.7	8	[1.0]	[0.67-1.4]	29	0.96	0.71-1.3	47
Liver and biliary tract	1.4	0.38-3.6	4	[1.9]	[0.86-3.6]	9	[1.9	[0.91-3.5]	10	0.94	0.40-1.9	8
Primary liver cancer				2.3	0.74-5.3	5	[1.1]	[0.14-4.0]	2			
Biliary tract				1.6	0.43-4.0	4	[2.2]]	[0.96-4.4]	8			
Cervix	NR			2.4	1.1-4.8	8	2.2	0.61-5.7	4	0.61[a]	0.25-1.3	7
Prostate	1.3	0.84-1.8	26	1.4	0.73-2.4	13	0.80	0.50-1.2	22	0.93	0.60-1.4	25
Kidney	1.2	0.42-2.5	6	0.87	0.32-1.9	6	[1.1]	[0.46-2.1]	8	0.93	0.48-1.6	12
Urinary bladder	1.0	0.44-2.0	8	0.82	0.27-1.9	5	[1.4]	[0.70-2.5]	11	1.3	0.74-2.0	17
Skin	2.4	1.0-4.7	8	NR			[1.0][b]	[0.38-2.3]	6	0.7[c]	0.29-1.5	7
Brain and nervous system	NR			1.1	0.50-2.1	9	[0.78]	[0.36-1.5]	9	0.78	0.42-1.3	13
Lymphohaematopoietic system				1.5	0.92-2.3	20	[0.94]	[0.66-1.3]	37	0.78	0.56-1.1	38
Non-Hodgkin's lymphoma	[1.5][d]	0.5-3.6	5	1.8[d]	0.78-3.6	8	[1.3][d]	[0.68-2.1]	14	0.82	0.44-1.4	13
Hodgkin's disease	1.1	0.03-6.0	1	1.7	0.35-5.0	3	[0.87]	[0.24-2.2]	4	0.73	0.20-1.9	4
Leukaemia	NR			1.1	0.35-2.5	5	[0.73][e]	[0.37-1.3]	11	0.82[d]	0.47-1.3	16

SIR, standardized incidence ratio; CI, confidence interval; Obs, observed; SMR standardized mortality ratio; NR, not reported
[a] Female genital organs
[b] Malignant melanoma
[c] Includes five cases of malignant melanoma
[d] Including ICD 202
[e] Including aleukaemia

Table 2. Cohort studies of cancer in people exposed to trichloroethylene

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Lindbohm et al. (2009) Finland	1.2 million economically active Finns born 1906-1945 from the census in 1970 .Incident cases (n=2474) between 1971 and 1995 identified from the Cancer Registry	Job-exposure matrix based on longest-held occupation in census 1970. Exposure to "**chlorinated solvents**"	Primary liver cancer	None <5 ppm years 5-49 ≥50	1618 20 44 9	1.00 reference 1.25 (0.80–1.95) 1.13 (0.84–1.53) 2.65 (1.38–5.11)	Age, period, job-specific social class, alcohol consumption and smoking from population surveys	Exposure to trichloroethylene not analysed separately. Exposure to chlorinated solvents was assumed to occur among "metal platers and coaters, building painters, printers, printerworkers NEC, paint/pharmaceutical manufacturers, and launderers
			Hepato-cellular cancer	None <5 5-49 ≥50	892 11 27 7	1.00 reference 1.23 (0.68–2.24) 1.22 (0.83–1.80) 3.59 (1.71–7.57)		
Radican et al. (2008) Utah, USA Hill Airforce Base cohort 1952-1990. Extension of Blair et al. 1998, which was an extension of the Spirtas et al. (1991), cited in IARC (1995).	14455 aircraft maintenance workers employed for at least 1 year in 1952-1956 in Utah, USA. Mortality 1952-2000. 10732 males, 8580 deaths, out of which 4320 males were analysed	Each job categorized as low intermittent, low continuous, peak infrequent, peak frequent to give a cumulative TCE exposure score for each worker	Males					
			all causes	lowest tertile second tertile highest tertile	1419 922 1287	1.00 (0.92-1.08) 1.05 (0.97-1.15 1.09 (1.01-1.18)	Cox regression model time variable age, covariable = race. Referent group males of the cohort with no chemical exposure	Expected numbers based on Utah rates. For female workers,. no consistent picture emerges, and the confidence intervals are large. Female breast hazard ratio in the three exposure tertiles 1.57, 1.01, and 1.05
			all cancer	lowest tertile second tertile highest tertile	297 183 249	1.11 (0.93-1.33) 1.11 (0.91-1.35) 1.13 (0.94-1.36)		
			oesophagus (150)	lowest tertile second tertile highest tertile	7 3 5	1.84 (0.48-7.14) 1.33 (0.27-6.59) 1.67 (0.40-7.00)		
			Colon (153)	lowest tertile second tertile highest tertile	30 20 26	1.46 (0.80-2.65) 1.57 (0.82-3.01) 1.52 (0.82-2.80)		
			Rectum (154)	lowest tertile second tertile highest tertile	4 0 4	0.76 (0.19-3.05) - 0.96 (0.24-3.85)		
			Liver primary (155.0)	lowest tertile second tertile highest tertile	4 0 4	3.28 (0.37-29.45) - 4.05 (0.45-36.41)		
			Pancreas (157)	lowest tertile second tertile highest tertile	17 8 14	0.97 (0.48-1.97) 0.74 (0.31-1.76) 0.97 (0.46-2.04)		
			Kidney (189.0)	lowest tertile second tertile highest tertile	10 1 5	1.87 (0.59-5.97) 0.31 (0.03-2.75) 1.16 (0.31-4.32)		
			NHL (200)	lowest tertile second tertile highest tertile	18 7 12	1.83 (0.79-4.21) 1.17 (0.42-3.24) 1.50 (0.61-3.69)		
			Multiple myeloma (203)	lowest tertile second tertile highest tertile	5 7 7	0.69 (0.21-2.27) 1.58 (0.53-4.71) 1.19 (0.40-3.54)		

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Zhao et al. (2005) rocket engine testing laboratory workers in southern California, USA	Cohort of males employed for ≥ 2 years 1950-80, followed for mortality (n=6044) 1950-2001 and for cancer incidence (n=5049) 1988-2000. Average duration of employment 16 years. Workers employed at nuclear facilities not included	Job exposure matrix based on individual working histories. Exposures to TCE, benzene, hydrazine, PAH, mineral oils assessed. Information on work on test stands not available.	site/ICD 9	cumulative TCE exposure score		RR incidence, zero years lag	Cox model variables time since first employment, socioeconomic status, age at event,	Six deaths and 6 incident cases of liver cancer not analysed. Lymphomas and leukemias analysed together, no association with TCE exposure. Results for kidney and bladder similar when zero or 20 year lag was applied. Point estimates lower but CI narrower when other exposures were excluded from the model.
			Esophagus & stomach 150-151	≤ 3 3 ≤score ≤ 12 ≥12	9 8 2	1.00 1.66 (0.62-4.41) 0.82 (0.17-3.95)		
			Colon& rectum 153-154	≤ 3 3 ≤score ≤ 12 ≥12	49 28 13	1.00 0.93 (0.51-1.50) 0.92 (0.49-1.72)		
			Pancreas 157	≤ 3 3 ≤score ≤ 12 ≥12	13 7 1	1.00 0.85 (0.33-2.17) 0.28 (0.04-2.14)		
			Kidney 189	≤ 3 3 ≤score ≤ 15 ≥15	6 6 4	1.00 1.87 (0.56-6.20) 4.90 (1.23-19.6)		
			Bladder 188	≤ 3 3 ≤score ≤ 12 ≥12	20 19 11	1.00 1.54 (0.81-2.92) 1.98 (0.93-4.22)		
			NHL & leukaemia 200-208 excl 2041	≤ 3 3 ≤score ≤ 15 ≥15	28 16 1	1.00 0.88 (0.47-1.65) 0.20 (0.03-1.46)		
Boice et al. (2006) rocket engine testing laboratory workers in southern California, USA	8372 workers employed 1948-1999 for no less than 6 months in the same facilities as studied by Zhao et al. (2005) followed for mortality 1948-1999. 2251 deaths, 2% lost to follow-up. For approx. 2.5% death certificate was not obtained.	Job exposure matrix based on individual working histories including information on work at individual testing facilities. TCE exposure was observed mainly among test stand mechanics during engine flush.	Site /ICD 9					There is apparently a marked overlap with the Zhao study
			All cancer	Potential exposure to TCE (engine flush) test-yr referent (cohort excluded test stand mechanics) 0 <4 ≥ 4	1168 89 18 42	Ref 0.82 (0.65-1.04) 1.07 (0.64-1.79) 0.99 (0.70-1.42)	Model adjusted for potential exposure to hydrazine	
			Esophagus / 150	All test stand mechanics				
				Exposure duration < 5 yrs	3	0.94 (0.19-2.75)		
				≥ 5 years	2	1.20 (0.15-4.35)		
			Stomach / 151	All test stand mechanics				
				Exposure duration < 5 yrs	5	1.24 (0.40-2.89)		
				≥ 5 years	5	2.19 (0.71-5.11)		
			Colorectal / 153-154	All test stand mechanics				
				Exposure duration < 5 yrs	11	1.00 (0.50-1.79)		
				≥ 5 years	8	1.27 (0.55-2.51)		
			Liver, biliary / 155,156	All test stand mechanics				
				Exposure duration < 5 yrs	3	1.01 (0.21-2.94)		
				≥ 5 years	1	0.66 (0.02-3.67)		
			Pancreas / 157	All test stand mechanics				
				Exposure duration < 5 yrs	3	0.51 (0.11-1.49)		
				≥ 5 years	2	0.62 (0.08-2.23)		
			Kidney / 189.0-189.2	All test stand mechanics				
				Exposure duration < 5 yrs	5	1.69 (0.55-3.95)		
				≥ 5 years	3	1.95 (0.40-5.71)		

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
				Potential exposure to TCE (engine flush) test-yr referent 0 <4 ≥ 4	 28 3 1 3	 Ref 1.21 (0.33-4.35) 2.51 (0.27-23.5) 3.13 (0.74-13.2)	Model adjusted for potential exposure to hydrazine	
Chang et al. (2003, 2005)	Retrospective cohort of 86868 workers employed 1978-1997 in an electronics factory in Northern Taiwan followed for mortality 1985-1997 and for cancer incidence in the 2005 study.	Chlorinated solvents (probably mainly TCE and tetra-chloroethylene)						Average age of workers at the close of the study: 39 years, average duration of employment: 1.6 years, less than one year for 65% of the cohort. Total number of cancer deaths 66. TCE known not to be used 1975-1991 (closure of the facility) but may have been used 1968-1975. Thre were no significant increases in risk for any tissue, although female breast cancer incidence was slightly elevated.
Raaschou-Nielsen et al. (2003) cohort of 347 Danish companies with documented use of trichloroethylene	40049 blue-collar workers with more than 3-month employment in 1968 or after from mandatory pension fund files. Cancer incidence in 1968-1997 from National Cancer Registry.	Categorization by duration of employment, time of hire, number of employees (separate studies showed exposure to have been higher in earlier years and in smaller enterprises).	All cancer	Cohort	2434	1.08 (1.04-1.12)		Figures are for males. Comparison to total Danish population is likely to lead to an overestimation of cancers associated with lower social class, notably those with an association with alcohol and tobacco use. Relative risks similar for females but confidence intervals larger. Overlap with Raaschou-Nielsen et al. 2001 not significant (2 common NHL
			Esophagus / 150; all Esophagus / 150, adenocarcinoma	Cohort Cohort Duration of employment (yr) <1 1-4.9 ≥5 Year of first employment Before 1970 1970-1979 1980 and later	40 23 6 9 8 8 10 5	1.1 (0.81-1.53) 1.8 (1.15-2.73) 1.7 (0.6 – 3.6) 1.9 (0.9 – 3.6) 1.9 (0.8 – 3.7) 1.5 (0.6 – 2.9) 2.0 (1.0 – 3.7) 2.2 (0.7 – 5.1)		
			Colon 153	Cohort	142	0.9 (0.77-1.08)		
			Rectum 154	Cohort	128	1.1 (0.95-1.35		
			Liver / 155.0 (ICD 7)	Cohort Duration of employment (yr) <1 1-4.9 ≥5 Year of first employment Before 1970	27 9 9 9 17	1.1 (0.74 – 1.64) 1.3 (0.6 – 2.5) 1.0 (0.5 – 1.9) 1.1 (0.5 – 2.1) 1.5 (0.9 – 2.4)		

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
				1970-1979 1980 and later	7 3	0.8 (0.3 – 1.6) 0.9 (0.2 – 2.6)		cases).
			Pancreas 177	Cohort	66	1.1 (0.85 – 1.39)		
			RCC / 180	Cohort Duration of employment (yr) <1 1-4.9 ≥5 Year of first employment Before 1970 1970-1979 1980 and later	68 14 25 29 44 16 8	1.2 (0.93 – 1.51) 0.8 (0.5 – 1.4) 1.2 (0.8 – 1.7) 1.6 (1.1 – 2.3 1.7 (1.2 – 2.3) 0.7 (0.4 – 1.2) 0.9 (0.4 – 1.7)		
			Bladder 181	Cohort	203	1.0 (0.89 – 1.18)		
			NHL / 200, 202	Cohort Duration of employment (yr) <1 1-4.9 ≥5 Year of first employment Before 1970 1970-1979 1980 and later	83 23 33 27 38 35 10	1.2 (0.98 – 1.52) 1.1 (0.7 – 1.6) 1.3 (0.9 – 1.8) 1.4 (0.9 – 2.0) 1.4 (1.0 – 2.0) 1.3 (0.9 – 1.8) 0.7 (0.3 – 1.3)		
Hansen et al. (2001) Denmark 1968-1996	Cohort of 803 workers monitored (industrial hygiene or biological monitoring) for exposure to TCE 1947-1986 linked to Danish Cancer registry for cancer incidence. Expected figures from national Danish incidence rates by sex, 5-year age group and calendar year.	Cumulative exposure categorized by job history and air/urine measurements.	Males	cohort			There was no adjustment for alcohol consumption and no sampling for HPV infection	In women, cancer of the lung SIR 0.7 (0.01-3.8), colon 0.7 (0.01-4.0), uterine cervix 3.8 (1.0-9.8), breast 0.9 (0.2-2.3). For other cancers in women, expected numbers <1 except for skin (other cancer), ICD 191, 2.3 expected, 0 observed.
			All cancer		109	1.0 (0.9-1.3)		
			Esophagus		6	4.2 (1,5-9.2)		
			Colon		5	0.7 (0.2-1.6)		
			Rectum		7	1.3 (0.5-2.7)		
			Liver & biliary (155)		5	2.6 (0.8-6.0)		
			Pancreas		3	1.0 (0.2-3.0)		
			Kidney (180)		3	0.9 (0.2-2.6)		
			Bladder (181)		10	1.1 (0.5-2.0)		
			NHL (200,202)		8	3.5 (1.5-6.9)		
Boice et al. (1999) Burbank California Lockheed 1960-1996	Cohort of 77965 workers employed ≥ 1 year between 1960 and 1996. Average follow-up 24.2 years. 0.7% lost to follow-up. 20236 deaths, missing cause of death for 1.7%.	Job history from work history cards, exposure assessment from task descriptions (since 1945), by walk through and industrial hygiene	All causes	potential routine exposure to TCE	1110	0.83 (0.79-0.88)		It was common for workers to be exposed to many substances. For example, over 70% of workers who used TCE or PCE either routinely or
			All cancer		277	0.86 (0.76-0.97)		
			Esophagus (150)		7	0.83 (0.34-1.72)		
			Colon (153)		30	1.07 (0.72-1.52)		

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
		files (since 1974). Exposure classified as routine, intermittent or unlikely.	Rectum (154)		9	1.29 (0.59-2.45)		intermittently were also estimated to have had exposure to compounds containing chromate on a routine or intermittent basis.
			Liver (155, 156)		4	0.54 (0.15-1.38)		
			Pancreas (157)		7	0.41 (0.17-0.85)		
			Kidney (189.0-189.2)		7	0.99 (0.40-2.04)		
			Bladder (188, 189.3-189.9)		5	0.55 (0.18-1.28)		
			NHL (200,202)		14	1.19 (0.65-1.19)		
			Hodgkin's disease (201)		4	2.77 (0.76-7.10)		
Morgan et al. (1998) Hughes aircraft plant, Arizona. Update of the unpublished Wong & Morgan (1994) study.	Cohort of 20508 workers (13742 male, 6766 female) employed for ≥6 months between 1950 and 1985 followed through 1993. altogether 4052 deaths; 112 death certificates not located.	Estimated exposure for each job title and duration of job held were used to derive cumulative exposure (none, low, high).	All causes	TCE exposed subcohort low exposure high exposure	917 345 572	0.84 (0.79-0.90) 0.86 (0.77-0.95) 0,83 (0.77-0.91)		Expected numbers based on national rates 27 persons with missing information excluded from the cohort
			All cancer	TCE exposed subcohort low exposure high exposure	270 114 156	0.92 (0.81-1.03) 1.04 (0.86-1.25) 0.84 (0.71-0.98)		
			Rectum	TCE exposed subcohort low exposure high exposure	6 1 56	0.98 (0.36-2.13) 0.49 (0.01-2.74) 1.38 (0.45-3.21)		
			biliary passages & liver	TCE exposed subcohort low exposure high exposure	6 3 3	0.98 (0.36-2.13) 1.32 (0.27-3.85) 0.78 (0.16-2.28)		
			Pancreas	TCE exposed subcohort low exposure high exposure	11 5 6	0.98 (0.36-2.13) 0.95 (0.31-2.22) 0.84 (0.71-0.98)		
			kidney	TCE exposed subcohort low exposure high exposure	8 1 7	1.32 (0.57-2.60) 0.47 (0.01-2.62) 1.78 (0.72-3.66)		
			bladder	TCE exposed subcohort low exposure high exposure	8 1 7	1.36 (0.59-2.68) 0.51 (0.01-2.83) 1.79 (0.72-3.69)		
			all lymphatic & haematol.	TCE exposed subcohort low exposure high exposure	25 10 15	0.99 (0.64-1.47) 1.07 (0.51-1.96) 0.95 (0.53-1.57)		

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Ritz (1999) Fernald Feed Materials Production Center, Fernald, Ohio, USA	3814 white male employees employed ≥ 3 months between 1951 and 1972 and monitored for radiation followed Jan 1951- Dec 1989. Death certificates available for 1045 employees Average follow-up time31.5 yrs.	Job title and plant area-based expert assessment of exposure level to TCE, cutting fluids and kerosene at levels 1,2,3. No worker in TCE exposure group 3.	liver &biliary 155,156	light exposure, > 5 years medium exposure, > 5 years	3 1	1.90 (0.35-10.3) 8.82 (0.79-98.6)	Time since first hire, pay type, external and internal radiation dose, TCE "at different level" (probably meaning < 5 years in this case)	Persons lost to follow-up considered to be alive. About half of the TCE exposed workers were also exposed to kerosene. Cancer sites grouped (all hemato and lymphopoietic, esophagus and stomach). Brain and lymphopoeitic cancer incidences disappeared after adjusting for cutting fluid exposure.
			Hemato- and lympho-poietic	light exposure, > 5 years	15	1.85 (0.87-3.95)		
			Oesophagus and stomach	light exposure, > 5 years	8	1.03 (0.40-2.63)		
			Prostate	light exposure, > 5 years medium exposure, > 5 years	8 1	0.83 (0.33-2.09) 1.58 (0.20-12.5)		
			Brain	light exposure, > 5 years medium exposure, > 5 years	3 1	1.32 (0.28-6.17) 4.52 (0.49-41.5)		
Alexander et al. (2007)	**Meta-analysis** of 9 cohort studies that specifically analysed TCE exposure.		Liver and biliary combined	total cohorts SRRE	280	1.14 (0.93-1.39)		Anttila et al. (1995), Axelson et al. (1994), Blair et al. (1998), Boice et al. (1999, 2006), Morgan et al. (1998), Raaschou-Nielsen et al. (2003), Ritz (1999)
				TCE exposed subgroup	129	1.30 (1.09-1.55)		
			liver (primary)	total cohorts SRRE	52	1.37 (1.04-1.79)		
				TCE exposed subgroup	49	1.41 (1.06-1.87)		
Mandel et al. (2006)	Meta-analysis of 8 cohort studies with detailed information on TCE exposure.		NHL (200, 202)	USA studies total cohort TCE exposed subcohort highest TCE exposure Lowest TCE exposure longest TCE exposure Shortest TCE exposure		 1.00 (0.80-1.24) 1.25 (0.87-1.79) 0.90 (0.50-1.65) 1.00 (0.55-1.81) 1.21 (0.77-1.92) 1.10 (0.69-1.75)		Blair et al. (1998), Boice et al. (1999), Morgan et al. (1998)
				European studies total cohort TCE exposed subcohort highest TCE exposure Lowest TCE exposure longest TCE exposure Shortest TCE exposure		 1.84 (1,10-3,07) 1.86 (1,27-2,71) 2,96 (1,20-7,32 2,45 (1,39-4,32) 1,81 (1,09-2,99) 2,13 (0,86-5,26)		Anttila et al. (1995), Axelson et al. (1994), Hansen et al. (2001), Raaschou-Nielsen et al. (2003)
Alexander et al. (*2006*)	Meta-analysis of 7 cohort studies on multiple myeloma and leukaemia and TCE exposure.		Multiple myeloma		62	1.05 (0.80-1.38)		Blair et al. (1998), Boice et al. (1999), Raaschou-Nielsen et al. (2003), Axelson et al. (1994), Anttila et al. (1995), Hansen et al. (2001), Morgan et al. (1998)
			Leukaemia		131	1.11 (0.93-1.32		

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Ojajärvi et al. (2001)	Meta-analysis of cohort and case-control studies on TCE and pancreatic cancer					1.24 (0.79-1.97)		Spirtas et al. (1991), Siemiatycki (1991), Greenland et al. (1994), Axelson et al. (1994), Anttila et al. (1995)
Ecological study								
Morgan and Cassady (2002) city of Redllands, California	Cancer cases in 1988-1998 from the population of 13 census tracts potentially exposed to TCE and perchloric acid via drinking water	Historical records of well water and water pipelines	all cancer	resident of potentially contaminated area at time of cancer diagnosis	3098	0.97 (0.93-1.02)		
			liver and bile duct		28	1.29 (0.74-2.05)		
			kidney and renal pelvis		54	0.80 (0.54-1.12)		
			NHL		111	1.09 (0.84-1.38)		

Table 3. Case–control studies of trichloroethylene and cancer

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI); number of exposed cases	Adjustment for potential confounders	Comments
Lee et al. (2003) Northern Taiwan 1966-1997	Stomach (151)	Cancer cases 1966-1997 from household registration offices in two villages in the vicinity of a factory contaminating the ground water with chlorinated solvents	Mortality odds ratio calculated using cardiovascular and cerebrovascular deaths in same villages	Village well contaminants; highest concentrations of perchloroethylene and trichloroethylene.	Exposed / non-exposed; MOR	2.18 (0.97-4.89); 39	age and period of exposure	
	Colorectal (153-154)					0. 83 (0.24-2.89); 26		
	Liver (155)					2.57 (1.31-3.17); 53		
Kernan et al. (1999) 24 US States 1984-1993	Pancreas ICD 9 157)	From death certificates, 63097 deceased persons	252386 non-cancer deaths frequency-matched by state, race, gender, and 5-year age group	Coded occupation and industry from usual occupation on death certificate linked to job task-exposure matrix for 12 solvents: intensity and probability scored as low, medium, high.	white males		age, marital status, metropolitan, and residential status	Figures similar for black males and white females. For black females, SMR for medium probability of exposure was 2.3 (1.3-4.0) and 0.9 (0.7-1.2) for high exposure. SMR for different intensities of exposure did not exceed 1.1 in any group.
					low probability of exposure to TCEi	0.9 (0.9-1.0); 3652		
					medium probability of exposure	1.3 (1.1-1.5); 910		
					high probability of exposure	1.0 (0.8-1.2); 735		
Dumas et al. (2000) Montreal, Canada 1979-1985	Rectal	257 histologically confirmed incident cases (84.5% of those eligible) from 19 major hospitals in Montreal area. Proxy respondents 15.2%	1295 subjects with cancers at sites other than the rectum, lung, colon, rectosigmoid junction, small intestine,and peritoneum (82% of those eligible). Proxy respondents 19.7%	Questionnaire on life style factors and another on job history. Job history was evaluated by a team of chemists and hygienists and translated into occupational exposures.	Trichloroethylene exposure any substantial any, adjusted in addition to other studied exposures	 2.0 (1.0-3.9); 12 0.9 (0.3 -3.2); 3 1.6 (0.8-3.5); 12	Logistic regression analyses adjusted for age, education, cigarette smoking, beer consumption, body mass index, and respondent status	

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI); number of exposed cases	Adjustment for potential confounders	Comments
Fritschi & Siemiatycki (1996)	Melanoma of the skin	103 histologically confirmed incident cases (83% of those eligible) from 19 major hospitals in Montreal area. Proxy respondents 12%	533 subjects with cancers at sites other than the lung (82%of those eligible) together with 533 healthy controls from electoral lists or random digit dialling (71% response rate). Proxy respondents 22 and 13% for cancer and healthy controls, respectively.	Questionnaire on life style factors and another on job history. Job history was evaluated by a team of chemists and hygienists and translated into occupational exposures.	Trichloroethylene Non-substantial exposure Any exposure Substantial exposure	 3.8 (1.1-13.6); 4 3.6 (1.5-9.1);8 3.4 (1.0-12.3); 4		
Charbotel et al. (2006) valley of Arve in France	Renal cell carcinoma ICD 189	86 cases (19 deceased) (1993-2003) from hospitals and practitioners. Participation rate 74%.	316 controls from the hospitals and practitioners from the same area, gender- and age (2 yrs) matched. Participation rate 78%.	Questionnaire-based industrial hygienist assessment.	Non-exposed Low/medium no peaks Low/medium + peaks High no peaks High+ peaks	1.0; 49 1.35 (0.69–2.63); 12 1.61 (0.36–7.30); 3 1.76 (0.65–4.73); 8 2.73 (1.06–7.07); 8	Smoking (4 classes), BMI (3 classes).	
					Non-exposed Low/medium no peaks Low/medium + peaks High no peaks High+ peaks	1.0; 44 0.90 (0.27–3.01); 4 1.34 (0.13–14.02); 1 2.74 (0.66–11.42); 4 3.80 (1.27–11.40); 7		Only living patients <80 years of age included. Analysis restricted to persons with high confidence in exposure assessment
Brüning *et al.* (2003) Arnsberg, Germany June 1992-April 2000	RCC	134 histologically confirmed cases from Karloinen Hospital. 87% response rate. 21 next of kin interviews	401 living hospital controls from local departments of surgery and of geriatrics. No next of kin interviews	Each job held for at least 1 year assessed for chemical exposures using the CAREX database. Self-reported exposure	Self-reported exposure to TCE	2.47 (1.36-4.47); 25	Age, gender, smoking	Not overlapping with the Vamvakas et al. (1998) study. Significant associations withlife-time exposure to aromatic amines, asbestos, chromates, cutting oils, diesel fumes/fuels, PAHs, soot, tar & mineral oils, welling fumes

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI); number of exposed cases	Adjustment for potential confounders	Comments
Pesch et al. (2000a) 5 Centres in Germany 1991-1995	RCC	935 (570 males, 365 females, 95% histologically confirmed). Response rate 88%.	4298 frequency matched (region, sex, age) controls from population registries. Response rate 74%.	Interview on job titles held ≥ 1 yr and job tasks. Exposure estimated from 1)British JEM,. 2) German JEM, a Job-task-exposure matrix (JTEM)	German JEM trichloroethylene, males medium high substantial females medium high substantial	 1.1 (0.9-1.4); 135 1.1 (0.9-1.4); 138 1.3 (0.9-1.8); 55 1.2 (0.8-1.8); 28 1.3 (0.8-2.0); 29 0.8 (0.3-1.9); 6	smoking: pack years & smoking status: never, time since stopping, smoker	Exposure categorized as 30, 60 and 90th percentile of the exposure of the exposed controls (medium, high, substantial, respectively)
					JTEM trichloroethylene, males medium high substantial females medium high substantial	 1.3 (1.0-1.8); 68 1.1 (0.8-1.5); 59 1.3 (0.8-2.1); 22 1.3 (0.7-2.6); 11 0.8 (0.4-1.9); 7 1.8 (0.6-5.0); 5		
Dosemeci et al. (1999) Minnesota, USA 1988-1990	RCC	438 histologically confirmed cases and with complete personal occupational history interview (273 men and 165 women) aged 20-85 years from Minnesota Cancer Surveillance System.	687 age- and gender stratified controls (462 men and 225 women) through random digit dialling (age group 40-65) or systematic sampling of Health and Welfare Financing Administration	NCI JEM for chlorinated solvents from for the most recent and for the usual occupation and in 13 predetermined hazardous jobs.	Men		Age, gender (for total) smoking, hypertension and/or use of diuretics and/or anti-hypertension drugs and body mass index	Occupational history limited: no assessment of probability or intensity of exposure
					All solvents	0.93 (0.7–1.3); 91		
					Chlorinated solvents	0.94 (0.7–1.3); 70		
					Trichloroethylene	1.04 (0.6–1.7); 33		
					Women			
					All solvents	2.29 (1.3–4.2); 35		
					Chlorinated solvents	2.08 (1.1–3.9); 29		
					Trichloroethylene	1.96 (1.0–4.0); 22		
Vamvakas et al. (1998) North Rhine Westphalia, Germany	RCC	58 living histologically verified cases (39 males) diagnosed in a hospital in 1987-1992 (85%	84 controls (55 males) from accident wards in three other hospitals in the same area in 1993.	Non-blinded questionnaire-supported interview on	Exposure category no exposure	 1.0; 39	Age and diastolic blood pressure	Cases on average 11 years older than controls. Study design and
					+	6.61 (0.50-87.76); 2		
					++	11.92 (2.55-55.60); 9		

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI); number of exposed cases	Adjustment for potential confounders	Comments
		response rate).	Ultrasonographically no renal tumours detected. Response rate 75%.	occupations and occupational exposures and other risk factors.	+++	11.42 (1.96-66.79); 8		interpretation criticized in Green & Lash (1999) and Mandel (2001). The authors respond to the former in Vamvakas et al. (2000) and to the latter in Vamvakas et al. (2001)
Pesch et al. (2000b)	Urothelial cancer	1035 cases (704 males, 331 females, 95% histologically confirmed). Response rate 84%.	4298 frequency matched (region, sex, age) controls from population registries. Response rate 74%	Interview on job titles held ≥ 1 year and job tasks. Exposure estimated from 1) British JEM, and 2) German JEM, a Job-task-exposure matrix (JTEM)	German JEM trichloroethylene, males medium high substantial females medium high substantial	 1.1 (0.8-1.3); 154 1.1 (0.9-1.4); 182 1.3 (0.9-1.7); 68 1.0 (0.6-1.7); 21 1.6 (1.0-2.5); 32 0.6 (0.2-2.3); 3	smoking: pack years & smoking status: never, time since stopping, smoker	Bladder cancer contributed 90.2% of all cases in males, 84.3% among females Exposure categorized as 30, 60 and 90th percentile of the exposure of the exposed controls (medium, high, substantial, respectively)
					JTEM trichloroethylene, males medium high substantial	 0.8 (0.6-1.2); 47 1.3 (0.9-1.7); 74 1.8. (1.2-2.7; 36		
Miligi et al. (2006) 8 areas in Italy	Non-Hodgkin's lymphoma	1428 incident cases diagnosed in 1991-1993 in persons 20-74 years of age. 83% participation rate.	Random sample of 1246 from population registry in the general population in the same areas stratified by sex and 5-yr age groups. 73% participation rate	Interviewer-administered standardized questionnaire and exposure assessment by job exposure matrix.	Very low/low vs Medium/high	0.8 (0.5-1.3); 35 1.2 (0.7-2.0); 35	Sex, age, education, study area	Proxy interview for 15% of the cases. No association with duration of exposure. Association of Hodgkin's disease assessed for chlorinated solvents.

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI); number of exposed cases	Adjustment for potential confounders	Comments
Persson et al. (1989) Örebro, Sweden	NHL	106 incident cases diagnosed 1964-1986 alive in 1986. Approx 88% response rate.	175 referents from the same area, a subset of referents from an earlier study. Approx 83% response rate	Questionnaire with 10 questions on occupational exposures	high vs low exposure	1.5 (not given); 8	crude OR	Fisher's exact test p =0.18 Logistic OR considering other exposures only reported for the group of organic solvent exposure. Crude OR higher for all other organic solvents studied.
Nordström et al. (1998) Sweden	Hairy cell leukaemia (subgroup of NHL)	111 incident male cases 1987-1993 from the Swedish Cancer Registry. 91% response rate.	400 age-matched control from the population registry. 83% response rate.	Mailed questionnaire on a variety of exposures with duration of ≥ 1 day with 1-year latency	Exposure vs none	1.5 (0.7-3.3); 9	univariate analysis	More strongly elevated OR observed for "all solvents", white spirit, paint, turpentine, aviation fuel, "other solvents".
Seidler et al. (2007) Six regions in Germany		710 (participation rate 87.4%) incident cases of lymphoma, ages 18-80 from "all regional hospitals and ambulatory physicians diagnosing and treating malignant lymphomas". 55% males, 45% females.	One gender, region and age (1 year) matched population control for each case from population registration office. Participation rate 44.3%.	Interview-based occupational history. For occupations held ≥1 year, estimation of intensity (low, medium, high as 30, 60 and 90th percentile of exposed controls) and frequency of exposure by trained industrial physician.	cumulative exposure in ppm years		age, sex, region, smoking in pack years, alcohol consumption in g/d	
	All lymphoma				0 ≤4.4 4.4-≤35 >35	1.0; 610 0.7 (0.4-1.1); 40 0.7 (0.5-1.2); 32 2.1 (1.0-4.8); 21		
	Hodgkin's-disease.				0 ≤4.4 4.4-≤35 >35	1.0; 104 0.4 (0.2-1.1); 6 0.4 (0.1-1.4); 3 2.0 (0.4-10.5); 2		
	B-NHL				0 ≤4.4 4.4-≤35 >35	1.0; 474 0.7 (0.5-1.2); 32 0.8 (0.5-1.3); 27 2.3 (1.0-5.3); 17		
	T-NHL				0 ≤4.4 4.4-≤35 >35	1.0; 27 0.7 (0.2-3.3); 2 1.1 (0.2-5.1); 2 4.7 (0.8-26.1); 2		
	Multiple myeloma (subentity of B-NHL)				0 ≤4.4 4.4-≤35 >35	1.0; 62 0.5 (0.2-1.9); 3 1.0 (0.4-2.7); 8 0.7 (0.1-5.5); 1		

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI); number of exposed cases	Adjustment for potential confounders	Comments
Childhood cancer								
De Roos et al. (2001a) 139 participating hospitals in USA and Canada 1992-1994	Childhood neuro-blastoma	568 cases ≤ 19 yrs of age (average age, 2.2 years) with newly diagnosed neuroblastoma. 73% response rate.	one control/case by random digital dialling matched on date of birth. 71% enrollment rate	interview with father and mother of life style and jobs held during 2 years before the birth. Industrial hygienist verified all identified exposures	Maternal exposure to halogenated hydrocarbons Paternal exposure to trichloroethylene	0.7 (0.2 – 2.1); 6 0.9 (0.3-2.5); 7	child age, maternal race, age, education	Occupational interviews available for 532 matched mother pairs and 232 father pairs. Results unchanged in hierarchical analysis (De Roos et al. 2001b)
Kerr et al. (2000) New York State excl. NY City 1976-1987	Childhood neuro-blastoma	183 histologically confirmed newly diagnosed cases 0-14 years of age. 85% response rate.	372 controls from NY state birth register matched on year of birth. 87% response rate	structured telephone interview of the mother on job titles and 25 potential carcinogens	Maternal exposure to TCE Paternal exposure to TCE	3.1 (0.4-27.6); 3 1.5 (0.6-3.9); 9		Mothers of cases and controls were similar with respect to education, nativity, religion, parity, gravidity, breast-feeding, alcohol, and cigarette use during pregnancy. Case and control fathers were similar with regard to several sociodemo-graphic variables including age at child's birth, education, and nativity. Interview not blinded.
Shu et al. (1999) Children's Cancer Group in USA and Canada 1989-1993	Childhood acute lymphocytic leukaemia	1914 newly diagnosed cases ≤ 15 yrs of age (92% response rate).	1987 individually matched (age, race, telephone area code) by random digit dialling (76.5% response rate).	Structured interview of mother and father on life-style, environmental exposures, occupational exposures.	Maternal exposure preconception during pregnancy postnatally Paternal exposure preconception during pregnancy postnatally.	1.8 (0.6–5.2); 9 1.8 (0.5–6.4); 6 1.4 (0.5–4.1); 9 1.1 (0.8–1.5); 100 0.9 (0.6–1.4); 56 1.0 (0.7–1.3); 77	paternal education, race, family income, age, and sex of the index child	positive associations (statistically significant or not) of ALL with maternal chemical exposure were observed with 32 of the 44 exposures studied.
Costas et al. (2002) Woburn, Massachusetts 1969-1986	Childhood leukaemia	Cluster of 21 leukaemias in persons < 19 years of age in an industrially contaminated area.	Two controls/case from records of area public school, matched race, sex, date of birth.	Modelled probability of exposure to water from two	Exp. 2 yrs before conception to diagnosis	2.39 (0.54-10.59);16	socio-economic status, maternal smoking during pregnancy, maternal age at birth	Water also contaminated with arsenic, tetrachloroethylene

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI); number of exposed cases	Adjustment for potential confounders	Comments
		Response rate 19/21.	Response rate not given.	identified contaminated wells	2 yrs before conception	2.61 (0.47-14.37); 8	of child and breast-feeding	and chloroform. No excess leukaemia during 4 years following the study. Previous study with 2/3 of the cases and a different water contamination model found an association of leukaemia and exposure to contaminated water after the birth but not during pregnancy.
					Birth to diagnosis	1.18 (0.28-5.05); 12		
					During pregnancy	8.33 (0.73-94.67); 10		
Mechanistic studies on RCC with case-control design								
Brüning et al. (1999) Dortmund, Germany	Renal damage in TCE-exposed RCC patients.					N tubular damage/ N total		
					healthy controls	11/100		
					RCC /No TCE exposure	23/50		
					RCC / TCE exposure	38/41		
Bolt et al. (2004) Arnsberg, Germany	Urinary excretion of α1-micro-globulin TCE-exposed RCC patients,	Cases from the Brüning et al. (2003) study				Abnormal α1-MC %		
					RCC non-exposed	48.1		
					RCC, exposed	85.0		
					Controls, non-exposed	44.6		
					Controls, exposed	38.9		
Brüning et al. (1996) Dortmund, Germany	GST poly-morphism among TCE--exposed RCC patients.	45 histologically confirmed cases heavily exposed to TCE	48 referents with similar exposure history to TCE		GSTM1+ GSTT1+	2.74 (1.18-6.63);27 4.16 (1.16-14.91); 42		
Brüning et al. (1997) Dortmund, Germany	VHL mutations in cancerous tissue in TCE-exposed RCC patients.	23 cases histologically confirmed cases heavily exposed to TCE	No referents			All cases had mutations in the VHL gene		

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI); number of exposed cases	Adjustment for potential confounders	Comments
Brauch et al. (1999) Dortmund, Germany	VHL mutations in cancerous tissue in TCE-exposed RCC patients.	Vamvakas et al. (1998) study cases collected 1987-1992 in Arnsberg, North Rhine Westphalia, Germany	RCC cases without TCE exposure from the same study		TCE exposure	N VHL mutations /N persons		The same RCC patients reported also in Brauch et al. 2003
					-	0/107		
					+	0/3		
					++	6/24		
					+++	7/17		
					-	2/21		
					++/+++	14/17		

Table 4. Carcinogenicity studies of inhalation exposure to trichloroethylene in laboratory animals

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Sprague-Dawley (M, F) 104 wk (then left untreated until natural death) Maltoni et al. (1986, 1988)	0, 540, 1620, 3240 mg/m^3 7 hr/d, 5 d/wk 130-145/sex/group	Testicular Leydig interstitial-cell tumours: 6/135, 16/130, 30/130, 31/130 (M)	$p < 0.05$ (low dose) $p < 0.01$ (mid dose) $p < 0.01$ (high dose) $p < 0.001$ (trend)	99.9% pure no epoxies
		Kidney tubular adenocarcinoma: 0/135, 0/130, 0/130, 4/130 (M) No evidence in females	not analysed	
Rat, Sprague-Dawley (F) 104 wk Fukuda et al. (1983)	0, 270, 810, 2430 mg/m^3 7 hr/d, 5 d/wk 49-51 per group	No evidence		99.8% pure 0.13% carbon tetrachloride 0.02% benzene 0.019% epichlorohydrin
Rat, Wistar (M, F) 18 months (killed at 36 months) Henschler et al. (1980)	0, 540, 2700 mg/m^3 6 hr/d, 5 d/wk 30, 30, 30, per sex	No evidence		> 99.9% pure 0.0015% triethanolamine no epoxies
Mouse, ICR (F) 104 wk Fukuda et al. (1983)	0, 270, 810, 2430 mg/m^3 7 hr/d, 5 d/wk 49-50 per group	Lung adenocarcinoma: 1/49, 3/50, 8/50, 7/46	$p < 0.05$ (mid dose) $p < 0.05$ (high dose) $p = 0.034$ (trend)	99.8% pure 0.13% carbon tetrachloride 0.02% benzene 0.019% epichlorohydrin
		Lung adenocarcinoma and adenoma combined: 6/49, 13/50, 11/46	not significant	

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F1 (M, F) 78 wk (then left untreated until natural death) Maltoni et al. (1986, 1988)	0, 540, 1620, 3240 mg/m^3 7 hr/d, 5 d/wk 90, 90, 90, 90, per sex	Lung tumours: 4/90, 6/90, 7/90, 15/90 (F) Liver hepatoma: 2, 3, 4, 8% (M and F combined)	$p < 0.05$ (high dose) significant at high dose (according to ECB, 2004)	99.9% pure no epoxies
Mouse, Swiss (M, F) 78 wk (then left untreated until natural death) Maltoni et al. (1986, 1988)	0, 540, 1620, 3240 mg/m^3 7 hr/d, 5 d/wk 90, 90, 90, 90, per sex	Lung tumours: 10/90, 11/90, 23/90, 27/90 (M) Liver adenoma/carcinoma combined: 4/90, 2/90, 8/90, 13/90 (M)	$p < 0.05$ (mid dose) $p < 0.01$ (high dose) $p < 0.05$ (high dose)	99.9% pure no epoxies
Mouse, NMRI (M, F) 18 months (killed at 30 months) Henschler et al. (1980)	0, 540, 2700 mg/m^3 6 hr/d, 5 d/wk 30, 30, 30, per sex	Lymphoma: 9/29, 17/30, 18/28 (F) No evidence in males	$p < 0.001$ (mid dose) $p = 0.01$ (high dose)	> 99.9% pure 0.0015% triethanolamine no epoxies
Hamster, Syrian 18 months (killed at 30 months) Henschler et al. (1980)	0, 540, 2700 mg/m^3 6 hr/d, 5 d/wk 30, 30, 30, per sex	No evidence		> 99.9% pure 0.0015% triethanolamine no epoxies

Table 5. Carcinogenicity studies of oral exposure to trichloroethylene in laboratory animals

Species, strain (sex) Duration of exposure Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Osborne-Mendel (M, F) 78 wk (killed at 110 wk) NCI (1976)	0, 549, 1097 mg/kg bw/day by gavage (time-weighted averages) 5 d/wk 20, 50, 50, per sex	No evidence		> 99% pure 0.19% epoxybutane 0.09% epichlorohydrin Survival was low in all groups, with only 3, 8 and 3 males, and 8, 13 and 13 females, surviving
Rat, Fischer 344/N (M, F) 103 wk NTP (1990)	0, 500, 1000 mg/kg bw/day by gavage 5 d/wk 50, 50, 50, per sex	Kidney tubular-cell adenocarcinoma: 0/48, 0/49, 3/49 (M) Kidney tubular-cell adenoma: 0/48, 2/49, 0/49 (M) No evidence in females	p = 0.028 (trend)	> 99.9% pure 8 ppm amine no epoxies
Rat, Osborne-Mendel (M, F) 103 wk NTP (1988)	0, 500, 1000 mg/kg bw/day by gavage 5 d/wk 50, 50, 50, per sex	Kidney tubular-cell adenocarcinoma: 0/50, 0/50, 1/50 (M) Kidney tubular-cell adenoma: 0/50, 6/50, 1/50 (M) No evidence in females	p = 0.007 (low dose)	> 99.9% pure 8 ppm amine no epoxies
Rat, Marshall (M, F) 103 wk NTP (1988)	0, 500, 1000 mg/kg bw/day by gavage 5 d/wk 50, 50, 50, per sex	Testicular interstitial-cell tumours: 17/46, 21/48, 32/48 (M) No evidence in females	p < 0.001 (survival adjusted, low dose) p < 0.001 (high dose)	> 99.9% pure 8 ppm amine no epoxies
Rat, ACI (M, F) 103 wk NTP (1988)	0, 500, 1000 mg/kg bw/day by gavage 5 d/wk 50, 50, 50, per sex	No evidence		> 99.9% pure 8 ppm amine no epoxies Survival was generally poor

Species, strain (sex) Duration of exposure Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, August (M, F) 103 wk NTP (1988)	0, 500, 1000 mg/kg bw/day by gavage 5 d/wk 50, 50, 50, per sex	No evidence		> 99.9% pure 8 ppm amine no epoxies Survival was generally poor
Rat, Sprague-Dawley (M, F) 52 wk (then left untreated until natural death) Maltoni et al. (1986)	0, 50, 250 mg/kg bw/day by gavage 4 or 5 d/wk 30, 30, 30, per sex	No significant increases Leukemia: 0/30, 2/30, 3/30 (M) No evidence in females	Not significant	99.9% pure no epoxies
Mouse, B6C3F1 (M) 78 wk (killed at 90 wk) NCI (1976)	0, 1169, 2339 mg/kg bw/day by gavage (time-weighted averages) 5 d/wk 20, 50, 50	Liver carcinoma: 1/20, 26/50, 31/48 Forestomach papilloma: 0/20, 0/50, 1/50	p = 0.004 (survival adjusted; low dose) p < 0.001 (survival adjusted; high dose)	> 99% pure 0.19% epoxybutane 0.09% epichlorohydrin
Mouse, B6C3F1 (F) 78 wk (killed at 90 wk) NCI (1976)	0, 869, 1739 mg/kg bw/day by gavage (time-weighted averages) 5 d/wk 20, 50, 50	Liver carcinoma: 0/20, 4/50, 11/47	p = 0.008 (survival adjusted; high dose)	> 99% pure 0.19% epoxybutane 0.09% epichlorohydrin
Mouse, B6C3F1 (M) 103 wk NTP (1990)	0, 1000 mg/kg bw/day by gavage 5 d/wk 50, 50	Liver adenoma: 7/48, 14/50 Liver carcinoma: 8/48, 31/50 Liver adenoma/carcinoma combined: 14/48, 39/50	p = 0.048 p < 0.001 p < 0.001	> 99.9% pure 8 ppm amine no epoxies
Mouse, B6C3F1 (F) 103 wk NTP (1990)	0, 1000 mg/kg bw/day by gavage 5 d/wk 50, 50	Liver adenoma: 4/48, 16/49 Liver carcinoma: 2/48, 13/49 Liver adenoma/carcinoma combined: 6/48, 22/49	p = 0.001 p = 0.002 p < 0.001	> 99.9% pure 8 ppm amine

Species, strain (sex) Duration of exposure Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, ICR:Ha Swiss (M, F) 18 months (killed at 24 months) Henschler et al. (1984)	0, 2.4 g/kg bw/day, no dosing for several wk due to toxicity, then 0 and 1.2 g/kg bw/day from wk 40 by gavage 5 d/wk 50, 50, per sex	Liver adenoma/carcinoma combined: 3/50, 6/50 (M) No evidence in females No forestomach tumours in either sex	No analysis	> 99.9% pure 0.0015% triethanolamine no epoxies [purified]
Mouse, ICR:Ha Swiss (M, F) 18 months (killed at 24 months) Henschler et al. (1984)	0, 2.4 g/kg bw/day, no dosing for several wk due to toxicity, then 0 and 1.2 g/kg bw/day from wk 40 by gavage 5 d/wk 50, 50, per sex	Forestomach carcinoma: Controls: 0/100 (a): 3/99 (b): 14/99 (c): 4/97 (d): 11/99		99.4% pure, 0.11% epichlorohydrin, 0.20% 1,2-epoxybutane [industrial grade] Purified, to which 0.8% epichlorohydrin was added Purified, to which 0.8% epoxybutane was added Purified, to which 0.8% epichlorohydrin and 0.8% epoxybutane were added As no forestomach tumours were seen in the group given TCE without epoxies (see row above), the epoxies were considered to be the cause of forestomach cancer
Mouse, ICR:Ha Swiss (M, F) 74 weeks Van Duuren et al. (1979)	0, 0.5 mg [about 20 mg/kg bw/day, assuming a mouse weighs 25 g] by gavage 1 d/wk 30, 30, per sex	No evidence of carcinogenicity (only lung, liver and (fore)stomach were examined.		Purity unspecified. IARC described the study conduct and reporting as inadequate.

Species, strain (sex) Duration of exposure Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, ICR (M, F) 16-18 months Wang et al. (2002)	0, 44, 106, 471 mg/L in drinking water Continuous 33-43 per sex per group	Liver adenoma/carcinoma combined: 1/23, 3/18, 4/15, 1/23 (M) Mammary gland adenocarcinoma: 0/24, 1/28, 0/23, 5/26 (F)	$p < 0.05$ (mid dose) $p < 0.05$ (high dose)	Purity unspecified The drinking water also contained, in mg/L, in the low-, mid- and high-dose groups: tetrachloroethylene (36, 90 and 607), 1,1-dichloroethane (6, 13 and 41), 1,1-dichloroethylene (1, 4 and 11), 1,1,1-trichoroethylene (2, 3 and 12), and chloroform (6, 8 and 14).

Table 6. Summary of TCE carcinogenicity studies in laboratory animals

Species, strain (sex)	Exposure route	Target organ (sex)	Reference
Rat, Fischer 344/N (M, F)	Gavage	Kidney (M)	NTP (1990)
Rat, Osborne-Mendel (M, F)	Gavage	Kidney (M)	NTP (1988)
Rat, Osborne-Mendel (M, F)	Gavage	No evidence (but poor survival)	NCI (1976)
Rat, Marshall (M, F)	Gavage	Testicular Leydig cell (M)	NTP (1988)
Rat, ACI (M, F)	Gavage	No evidence (but poor survival)	NTP (1988)
Rat, August (M, F)	Gavage	No evidence (but poor survival)	NTP (1988)
Rat, Sprague-Dawley (M, F)	Gavage	Leukemia? (M)	Maltoni et al. (1986)
Rat, Sprague-Dawley (M, F)	Inhalation	Kidney (M) Testicular Leydig cell (M)	Maltoni et al. (1986, 1988)
Rat, Sprague-Dawley (F)	Inhalation	No evidence	Fukuda et al. (1983)
Rat, Wistar (M, F)	Inhalation	No evidence	Henschler et al. (1980)
Mouse, B6C3F1 (M, F)	Gavage	Liver (M, F)	NCI (1976)

Species, strain (sex)	Exposure route	Target organ (sex)	Reference
Mouse, B6C3F1 (M, F)	Gavage	Liver (M, F)	NTP (1990)
Mouse, ICR:Ha Swiss (M, F)	Gavage	Liver (M)	Henschler et al. (1984)
Mouse, ICR:Ha Swiss (M, F)	Gavage	No evidence (only lung, liver and (fore)stomach were examined.	Van Duuren et al. (1979)
Mouse, ICR (F)	Inhalation	Lung	Fukuda et al. (1983)
Mouse, B6C3F1 (M, F)	Inhalation	Lung (F) Liver (M, F)	Maltoni et al. (1986, 1988)
Mouse, Swiss (M, F)	Inhalation	Lung (M) Liver (M)	Maltoni et al. (1986, 1988)
Mouse, NMRI (M, F)	Inhalation	Lymphoma (F)	Henschler et al. (1980)
Hamster, Syrian	Inhalation	No evidence	Henschler et al. (1980)

Document conclusions

A review of selected literature (1995-2009) on the carcinogenicity of trichloroethylene (TCE)

by P. Watts, D. Heederick and G.B.G.J. van Rooy

Table 7 – Overview of epidemiological evidence for TCE cancer risk and target tissue

	KIDNEY	NON-HODGKIN'S LYMPHOMA	LIVER BILIARY TRACT
IARC (1995)	no clear conclusion	evidence of modest increased risk	evidence of increased risk
EUROPEAN CHEMICAL BUREAU (2004)	limited evidence of increased risk	limited evidence of increased risk	
DRAFT US-EPA (2009)	convincing evidence of increased risk	compelling evidence of increased risk (less than kidney)	limited evidence
COHORT STUDIES (≥ 1995)	risk <2	risk <2	Risk <2
CASE CONTROL STUDIES (≥ 1995)	suggestion of increased risk (but limited studypower)	suggestion of increased risk (but limited study power)	–
AUTHORS' CONCLUSION	**elevated risk**	**elevated risk**	**elevated risk**

– No new studies

Note: There was no good information relating to exposure duration or or latency period before an increased risk was experienced.

Table 8 – Overview of TCE cancer studies in rodents, route and target tissue

	Kidney	Liver	Lung	Testes
Oral	Rats - *gavage* (low incidence of rare tumours)	Mice – *gavage*		Rats - *gavage* (inconclusive)
Inhalation	Rats (low incidence of rare tumours)	Mice	Mice (risk linked to accumulation of chloral hydrate in Clara cells)	Rats (inconclusive)
Authors' conclusion	Rats* (oral and inhalation)	Mice** (oral and inhalation)	Mice** (inhalation)	

* Rat: The mode-of-action by which these rat kidney tumours develop is unknown, and their relevance to humans is uncertain

**Mice: Based on available information on mechanism and mode of action, experts consider that the lung and liver tumours seen in TCE-exposed mice are not relevant to humans