Tetrachloroethylene (perc, tetra, PCE)

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Citation for most recent IARC review

IARC Monographs 63, 1995

Current evaluation

Conclusion from the previous Monograph:

Tetrachloroethylene (Perc) is *probably carcinogenic to humans (Group 2A)* with the working group finding limited evidence in humans for the carcinogenicity of Perc and sufficient evidence in experimental animals for the carcinogenicity of Perc. In making the overall evaluation, the Working Group considered the following evidence: (i) Although Perc is known to induce peroxisome proliferation in mouse liver, a poor quantitative correlation was seen between peroxisome proliferation and tumor formation in the liver after administration of Perc by inhalation. The spectrum of mutations in proto-oncogenes in liver tumors from mice treated with Perc was different from that in liver tumors from mice treated with trichloroethylene (TCE). (ii) The compound induced leukemia in rats. (iii) Several epidemiological studies showed elevated risks for esophageal and cervical cancer and non-Hodgkin lymphoma, which the working group stated was unlikely due to chance although confounding could not be excluded.

Exposure and biomonitoring

Perc is a solvent used for dry cleaning clothes and for metal cleaning and degreasing in a number of industries, including metal finishing, cleaning mining equipment, testing coal, cleaning animal coats in taxidermy, and cleaning and duplicating film (Gold et al., 2008). It is a volatile liquid at room temperature. The largest human exposure occurs indoors to workers in dry cleaning and metal finishing facilities. Near points of use, such as dry cleaners or industrial facilities, indoor exposure to Perc is more significant than outdoor exposure (U.S. EPA, 2001). Indoor air concentrations in apartments above a dry cleaning shop have been measured at up to 4.9 mg/m^3 (Verberk and Scheffers, 1980), whereas the historical overall arithmetic mean (AM) for personal Perc in the dry cleaning industry was 59 ppm (range 0 to 4636 ppm, n =1395) (Gold et al., 2008). Lower exposures since 1995 (McKernan et al., 2008) will necessitate new study designs to determine effects from lower exposures and apply methods to accommodate the reduction.

Perc can be converted to vinyl chloride under anaerobic conditions, which can contaminate soil and ground water, and vinyl chloride has been detecting in a dry cleaning facility (Vogel and McCarty, 1985; ATSDR, 2000).

The characteristics and uncertainties involved with Perc metabolism make establishment of biomarkers difficult. The Perc metabolite trichloroacetic acid (TCA) is not a good biomarker for Perc exposure. Better characterization of metabolism of Perc in the kidney is especially needed. End-exhaled alveolar air, for which a U.S. National Institute for Occupational Safety

and Health (NIOSH) method has been developed, integrates dermal and inhalation exposure (NIOSH, 1998).

Cancer in humans

(limited, vol 63, 1995)

Since the 1995 review one linkage and six case-control studies have been published and two cohort studies updated. Many of these studies have been reviewed (Mundt et al., 2003; Ruder, 2006). Table 3 below summarizes the case-control and cohort studies published since the IARC review in tabular format. [This is an updated version of the supplemental table to the review by Ruder (2006)]. The case-control studies provide some support for associations between Perc exposure and cancer of the breast, bladder, and lymphoma although most of the increases were not statistically sufficient. In work published since the reviews appeared, one case-control study found a statistically significant relative risk of bladder cancer among dry cleaners (Lynge et al., 2006), another found that the risks of lymphoma increased with increasing cumulative exposure to Perc, and that the trend was statistically significant for T cell NHL (Seidler et al., 2007). Another recent case-control study found no association between Perc exposure and risk of leukemia (Costantini et al., 2008).

The U.S. Environmental Protection Agency (EPA) recently published its draft Perc assessment (U.S. EPA, 2009). It concludes that overall, the epidemiologic evidence has associated Perc exposure with excess risks for a number of cancers, although a causal association has yet to be definitely established. Studies of Perc and cancer showed positive associations between exposure and cancer of the lymphoid system, esophagus, and cervix, with more limited evidence for cancer of the bladder, kidney, and lung. For both lymphoid and esophageal cancer, excess risk was observed in studies of human populations exposed to Perc and other solvents, including studies of exposures to dry cleaners or workers involved with degreasing metal parts. In these cases, average risks were doubled as compared with those of referents. Furthermore, studies of drinking water exposure also supported an association between lymphoid cancer and Perc and other solvents, as did case-control studies that assessed employment as dry cleaners. Chance and confounding by smoking were unlikely the sole explanations for the observed excesses in risks. Information was lacking on lifestyle and socioeconomic factors, which are indirect surrogates for human papilloma virus infection, a known risk factor for cervical cancer (U.S. EPA, 2009b).

More studies have been published since the 1995 IARC monograph regarding Perc but the type of meta-analysis suggested for TCE by various review panels and conducted for TCE have not been conducted for Perc. Ruder (2006) has published a compendium of Perc epidemiological studies to aid in this effort.

Cancer in experimental animals

(sufficient, vol 63, 1995)

Perc exposures have been associated with effects in a number of targets, which bring relevance to cancer targets as well. Targets of toxicity observed both in human and animal studies include the liver, kidney, CNS, reproductive system, and developing fetus. Affected organs are all sites of high metabolic activity. Humans were found to be particularly sensitive

for neurological effects, including decrements in vision or visuo-spatial function, and other neurobehavioral (cognitive) effects following inhalation exposure (U.S. EPA, 2009b).

The EPA laboratory animal database includes 10 lifetime rodent bioassay data sets that demonstrate increased cancer incidence. (Two additional study data sets, in male and female rats exposed orally, were inconclusive due to excessive mortality caused by pneumonia or Perc-related toxic nephropathy). Perc is a carcinogen in rodents in 10 of 10 lifetime bioassay data sets—including by oral and inhalation routes. It is reasonable to use these animal tumors as indicators of potential human cancer hazard (U.S. EPA, 2009b).

Hepatocellular adenomas and carcinomas in mice and mononuclear cell leukemia (MCL) in rats occurred in multiple lifetime rodent bioassays, and hemangioendotheliomas in male mice (JISA, 1993) and cancers of the kidney and brain (glioma) in male rats (NTP, 1986) occurred in single lifetime bioassays. Also known as hemangiosarcomas, hemangioendotheliomas are rare tumors of the epithelial lining of blood vessels. Although the dose-response relationships for kidney and brain tumors in male rats were not as strong as for the other cancers, and the increasing dose-response trend for kidney tumors was not statistically significantly, both tumor types were considered by EPA to be Perc-related and biologically relevant. The statistically significantly elevated incidences of hepatocellular carcinomas and adenomas in male and female mice and MCL in male and female rats are considered to be indicators of potential human health hazard, despite questions regarding high background incidences of these tumors in controls and mode of action (MOA) hypotheses. Kidney cancer and MCL in rats as indicators of a potential human cancer hazard appear reasonable, given the observations in the epidemiologic studies (U.S. EPA, 2009b).

Therefore, Perc is clearly carcinogenic in rats and mice. The apparent lack of site concordance across laboratory animal studies may be due to limitations in design or conduct in a number of rat bioassays and/or genuine inter-species differences in qualitative or quantitative sensitivity (i.e., potency). The data gaps in the epidemiology database may prevent identification of further site concordance between rodents and humans although there is some site concordance indicated by the current database.

Mechanistic issues

The large body of literature available for TCE is not available for Perc but the TCE literature can help inform mechanistic issues for Perc. The same mechanistic studies that inform TCE hypothesized MOAs apply to Perc as well (Caldwell et al., 2008; Guyton et al., 2009). Both TCE and Perc affect multiple targets. There are similarities in some of the targets identified for TCE that can help guide further study as well.

There are two major routes of metabolism for Perc: (1) the predominant oxidative pathway, which results in TCA and other urinary metabolites, as well as reactive intermediates and carbon dioxide; and (2) the glutathione (GSH) conjugation pathway, which results in *S*-(1,2,2-trichlorovinyl)- glutathione (TCVG) and *S*- (1,2,2-trichlorovinyl)-L-cysteine (TCVC) that are further processed to other chemically reactive products that can bind to tissue macromolecules. Further, metabolism of the GSH metabolites, including activation by beta lyase, occurs in the kidney. A potential exists for extrahepatic metabolism and formation of reactive metabolites at sites other than the liver and kidney. Although many steps in the oxidative metabolism of

Perc are well characterized in both animals and humans, not all proposed intermediates have been identified or detected (U.S. EPA, 2009b).

Less Perc (approximately 1 to 37%) than TCE is metabolized by the body (Zewdie et al., 2008). The concentrations of Perc metabolites and their contributions to toxicity are harder to determine than those of TCE metabolites. More studies needs to be done of the GSH pathway. There are fewer data on Perc GSH metabolites and those metabolites are less well characterized than TCE metabolites. Adequate physiologically based pharmacokinetic (PBPK) models have not been developed that allow for predictions of metabolism and differences in metabolism between species for a number of key metabolites. For genotoxicity, there is not adequate information describing the toxicity of the GSH pathway and there is not a full genotoxicity battery for such metabolites. Other endpoints such as epigenetic changes have not been studied. While systemic metabolism is small, local metabolism could drive toxicities. The studies of the TCE GSH pathway may help provide information on the types of studies needed for Perc. The toxicokinetic and genotoxicity data for GSH metabolites available for TCE that suggest systemic delivery to and *in situ* formation in the kidney are not as well developed for Perc.

Although a wealth of new data related to understanding the toxic effects caused by Perc exposure has been published over the past decade, the MOA is not yet sufficiently characterized, tested, or understood for any one of these adverse effects (U.S. EPA, 2009b). A number of alternative hypotheses are identified and examined as possible MOAs for liver and kidney toxicity. Hypothesized MOAs for MCL, neurotoxicity, and developmental/ reproductive effects are indirect and are based on experimental observations of exposures to agents other than Perc. The available evidence points to multiple hypothesized MOAs as being involved, and, in each case, no one MOA can be uniquely identified.

Both Perc and TCA have been shown to activate the peroxisome-proliferation activated receptor (PPAR)-α, however, metabolism to TCA does not fully explain Perc-induced liver tumors, suggesting that other metabolites or intermediates contribute to Perc liver toxicity. The same issues regarding the PPAR-α activation MOA described for DEHP and TCE apply to Perc (see TCE and DEHP reviews). For the kidney, induction of alpha-2μ-globulin occurs only at doses higher than the doses that induce kidney cancer in male rat bioassays, and it is not likely to have an important role in toxicity or tumor induction. Scientific evidence is more supportive of the possibility that reactive metabolites from the GSH conjugation pathway are in some way responsible for kidney toxicity. The MOA of Perc-induced leukemogenesis in rats is not well understood; specifically whether the parent compound, a metabolite, or several metabolites are involved (U.S. EPA, 2009b).

Heterogeneity among humans is another uncertainty associated with extrapolating the results between animal and human databases. The extent of inter-individual variability in Perc metabolism has not been characterized. Several enzymes of the oxidative and GSH metabolism, notably those coded by *CYP2E1, CYP3A4, GSTZ, GSTA, GSTM,* and *GSTT,* show genetic polymorphisms with the potential for variation in metabolite production. Such heterogeneity should be incorporated into the design of epidemiological studies to further clarify the association between Perc exposure and carcinogenesis.

Lifestyle will also affect Perc metabolism, especially activities that induce P450 enzymes. A number of inducers of *CYP* enzymes have been shown to affect Perc metabolism.

Research needs and recommendations:

Human cancer studies

The chief venue of Perc exposure is dry-cleaning shops, which generally have fewer than ten employees, so assembling an occupational cohort could be difficult. Dry-cleaning workers could be recruited through the media, rather than shop by shop with shop management as the gatekeeper. Morning exhaled-breath specimens on a Saturday, highly correlated with the previous day's time-weighted average (McKernan et al., 2008), could be the criterion for inclusion in a study. Assembling a new occupational cohort could be difficult. In the United States, dry-cleaning workers could be recruited by various means (see discussion of overarching issues for further discussion). Morning exhaled-breath specimens on a Saturday, highly correlated with the previous day's time-weighted average (McKernan et al., 2008), could be the criterion for inclusion in a study. Data from the two U.S. dry-cleaning cohorts could be pooled for analysis (Blair et al., 2003; Ruder et al., 2001) and for a cancer incidence study. Identification of cohorts of workers outside the United States should also be explored. The Nordic study could be expanded into a cohort (Lynge et al., 2006).

Brain tumor is also a potential target for Perc. The working group is aware of several large brain case-control studies (NCI, NIOSH, Interphone), which will be analyzed in the next year or two for an association between exposure to chlorinated solvents and risk of brain cancer (Inskip et al., 2001; Ruder et al., 2006; Cardis et al., 2007)

Genetic susceptibility studies

Future human studies should include genotyping of *GST* variants. Since the glutathione conjugation pathway is not active in *GST*-null individuals, it can be hypothesized that the liver and kidney cancer risk will be low among *GST*-null individuals and high among *GST*-nonnull individuals. Where possible, retrospective *GST* genotyping could be done on stored specimens. Genetic variants in the *CYP2E1, CYP3A4* and other genes coding for enzymes that metabolize Perc or its metabolites, should also be investigated. Studies should also be conducted using entire genome scans to identify new susceptibility genes.

Mechanistic studies

With respect to mechanistic data, a major research gap is that MOAs are not sufficiently characterized or tested, for any of the Perc-induced adverse effects. Studies are needed that evaluate the GSH pathway of Perc metabolism, including genotoxicity studies, and that identify intermediates in the oxidative pathway. Lastly, adequate PBPK models have not been developed that allow for predictions of metabolism and differences in metabolism between species for a number of key metabolites.

Immunologic mechanism may be involved in lymphomagenesis from solvents (Vineis et al., 2007) and this should also be an area of future research. Brain tumor is also a potential target for DCM, and Perc, and has not been adequately studied for TCE.

Clearly more epidemiological study and analysis of existing epidemiological literature is need for Perc. However, the further development of the types of mechanistic data and toxicokinetic data that have been elucidated for TCE needs to be developed for Perc and will aid in the design and interpretation of epidemiological studies.

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Table 3. Studies Evaluating Tetrachloroethylene Exposure and Cancer Risk

Reference	Study support/ affiliation	Study design	N	Outcome studied	Eligibility criteria	Exposure level	Other solvents, other exposures	Outcomes, ratio† (CI)	Study design issues
Aschengrau et al. 2003, Vieira et al. 2005 [Aschengrau, et al. 2003; Vieira, et al. 2005)	US NIEHS grant, US EPA grant	Case-control	672 female cases, 616 female controls	Breast cancer	Residents of 8 Cape Cod, Massachusetts, towns. Cases dx 1987-1993, Controls selected by random digit dialing or from Medicare roster	Relative delivered dose (RDD) or personal delivered dose (PDD) of PCE-contaminated piped-in water	Controlled for residence near dry cleaner, occ exp to PCE	RDD: with 0 latency adj OR 1.1 (0.8-1.4), PCE exp>75th percentile, adj OR 1.6 (1.1-2.4); with 5 years latency adj OR 1.2 (0.9-1.6), PCE exp>75th percentile, adj OR 1.6 (1.0-2.6); with 15 years latency adj OR 1.4 (0.9-2.3), PCE exp>75th percentile, adj OR 1.7 (0.7-4.3) PDD: with 0 latency adj OR 1.1 (0.8-1.4), with 5 years latency adj OR 1.2 (0.9-1.6), with 15 years latency adj OR 1.4 (0.9-2.3)	Exposure estimated wth model, no measurements
Bond et al. 1990 [Bond, et al. 1990]	Dow Chemical	Case-control nested in cohort	44 cases, 1,888 controls	Liver & biliary tract ca death	All employed in chemical production 1940-82, VS to 1982, controls randomly selected from cohort of 21,437	Work histories to classify by exp potential to 11 substances (any/none)	Carbon tet, chloroform, methylene chloride, 1,1,2-trichloro-ethane, vinyl chloride, PCB, dioxins, TCP, ethylene dibromide & dichloride	Exp: 13.6% cases, 11.3% controls RR 1.8 (0.8-4.3)	Workers could have had multiple exp, exp not quantified or qualified

Reference	Study support/ affiliation	Study design	N	Outcome studied	Eligibility criteria	Exposure level	Other solvents, other exposures	Outcomes, ratio† (CI)	Study design issues
Costantini et al. 2008, Miligi et al. 2006 [Costantini, et al. 2008; Miligi, et al. 2006]}	US NCI, Europe Against Cancer Programme, Italian Alliance Against Cancer	Case-control, population based	586 leukemia cases, 1278 controls; 263 multiple myeloma (MM) cases, 1100 controls; 1428 NHL & 304 HL cases, 1530 controls	Acute myeloid leukemia (AML), chronic lymphatic leukemia (CLL), MM, or lymphoma diagnosis	Cases: dx 1991-1993 age 20-74; Controls from municipal files, stratified by sex and 5-year age groups	Detailed occupation history, industrial hygienist blinded to case status assessed PCE exposure as very low-low (LO) or medium-high (HI)	Benzene, styrene, xylene, toluene, dichlorome-thane, TCE, 1,1,1-trichloro-ethane	Leukemia LO OR 0.6 (0.2-1.6), HI OR 1.0 (0.4-2.7); NHL LO OR 0.6 (0.3-1.2), HI OR 1.2 (0.7-2.0)	possible latency/lag issues, no solvent specific results presented for HL
Heineman et al. 1994, Gomez et al. 1994 [Gomez, et al. 1994; Heineman, et al. 1994][37,42]	US NCI	Case-control	300 male cases, 320 male controls	Brain tumor mortality	Died 1978-1981 hospital-confirmed astrocytic brain tumor or other causes (minus CVD, epilepsy, suicide, homicide, cirrhosis, some ca), NOK interviewed	JEM for probablity of exp, cum= duration weighted by probability. 35% estimated exp. to PCE	JEMs also for other chlorinated solvents	Low cum exp OR adj age, location 0.8 (0.5-1.4), med adj OR 1.3 (0.8-2.2), high adj OR 1.5 (0.7-3.2), test for trend not statistically significant	Low participation rate, interviewed <50% (300/ 741 cases, 320/ 741 controls). Low number with medium or high exp (35 cases, 35 controls)
Lynge et al. 2006 [Lynge, et al. 2006]	Halogenated Solvents Industry Alliance & Danish Medical Research Council	Case-control nested in retro-spective cohort	46,768 laundry & dry-cleaning workers	Cancer incidence	Listed in 1970 census as "laundry and dry-cleaning worker" in Denmark, Finland, Norway, or Sweden. Cases dx 1970-2001, controls frequency matched by country, sex, 5-year age group, 5 year calendar period	For known dry cleaners, duration of employment (1964-1979) in shop where they worked in 1970 as PCE surrogate (90% of shops used PCE)	No way to separate PCE use from white spirit or chlorofluoro-carbon use	Bladder cancer RRs: dry-cleaner 1.44 (1.07-1.93), "other in dry-cleaning" 1.08 (0.55-2.11). Cervical cancer RRs: dry-cleaning 0.98 (0.65-1.47), "other in dry-cleaning" 1.73 (1.00-2.97).	18% unclassifiable as to dry-cleaning status

Reference	Study support/ affiliation	Study design	N	Outcome studied	Eligibility criteria	Exposure level	Other solvents, other exposures	Outcomes, ratio† (CI)	Study design issues
Pesch et al. 2000a [Pesch, et al. 2000a]	German Federal Ministry of Research & Technology	Case-control	935 cases, 4298 population-based controls	RCC	Cases: German nationals dx 1991-1995. Controls frequency matched by region, sex, & age (5-year groups)	Occupational questionnaire, job-exposure matrices, job-task exposure matrices	Metals, paints, mineral oils, PAHs, asbestos	PCE JEM ORs: Medium exp males 1.4 (1.1-1.7), females 0.7 (0.4-1.3); high males 1.1 (0.9-1.4), females 1.1 (0.7-1.9); substantial males 1.4 (1.0-2.0), females 0.7 (0.3-2.2). PCE JTEM ORs: Medium exp males 1.2 (0.9-1.7), females 2.2 (0.9-5.2); high males 1.1 (0.7-1.5), females 1.5 (0.6-3.8); substantial males 1.3 (0.7-2.3), females 2.0 (0.5-7.8)	Combined OR (both sexes) not presented, trend tests (med-high-substantial) not done
Pesch et al. 2000b [Pesch, et al. 2000b]	German Federal Ministry of Research & Technology	Case-control	1035 cases, 4298 population-based controls	Urothelial carcinoma	Cases: German nationals dx 1991-1995. Controls frequency matched by region, sex, & age (5-year groups)	Occupational questionnaire, job-exposure matrices, job-task exposure matrices	Aromatic amines, paints & dyes, cutting fluids, PAHs, other chlorinated solvents	PCE JEM ORs: Medium exp males 1.1 (0.9-1.3), females 1.8 (1.0-3.0); high males 1.2 (1.0-1.5), females 1.0 (0.6-1.9); substantial males 1.4 (1.0-1.9), females 0.7 (0.2-2.5). PCE JTEM male ORs: Medium exp 1.0 (0.7-1.5). high 1.2 (0.8-1.7), substantial 1.8 (1.1-3.1)	Combined OR (both sexes) not presented, trend tests (med-high-substantial) not done
Seidler et al. 2007 [Seidler, et al. 2007]	German Federal Office for Radiation Protection	Case-control	710 lymphoma cases, 710 population-based controls	Lymphoma	Cases dx in 6 German regions age 18-80; controls matched on region, gender, and age ± 1 year	Complete occupational history assigned intensity & frequency of PCE by case-status blinded industrial physician	TCE, carbon tet, dichloro-methane, benzene, toluene, xylene, styrene	<9.1 ppm years adj OR 1.1 (0.5-2.3), 9.1-78.8 ppm years adj OR 1.0 (0.5-2.2), >78.8 ppm years adj OR 3.4 (0.7-17.3), trend p 0.12 T cell NHL trend p 0.01	No exposure measurements. Mixed exposures?

Reference	Study support/ affiliation	Study design	N	Outcome studied	Eligibility criteria	Exposure level	Other solvents, other exposures	Outcomes, ratio† (CI)	Study design issues
Anttila et al. 1995 [Anttila, et al. 1995]	Finnish Work Med Fund, US NIOSH grant	Linkage monitoring registry-cancer registry	292 men, 557 women	Cancer diagnosis	Monitored (serum) for exposure any time during 1974-1983; cancer diagnosed 1967-1992	Median 0.7 µmol PCE/L (men), 0.4 µmol PCE/L (women).	Small % also monitored for TCE, 1,1,1-trichloroethane	31 ca SIR 0.9 (0.6-1.3), 3 pancreas ca SIR 3.1 (0.6-9.0), 5 lung ca SIR 1.92 (0.6-4.5), 2 cervix ca SIR 3.2 (0.4-11.6), 2 kidney ca SIR 1.8 (0.2-6.6), 3 NHL SIR 3.8 (0.8-11.0)	60% only had 1-2 measurements (short duration employment?) . Low statistical power
Lynge & Thygesen 1990 [Lynge and Thygesen 1990]	Danish Cancer Registry	Linkage census-cancer registry	8567 women, 2033 men	Cancer diagnosis	Working in dry cleaning or laundry in 1970, diagnosed 1970-80	PCE most common from 1950s (0-100 ppm)	TCE for workclothes, chlorofluorocarbons for fur	No increase overall. Men: 131 ca SIR 1.3 (1.1-1.5), 9 pancreas ca SIR 2.4 (1.1-4.6). Women: 7 liver ca SIR 3.4 (1.4-7.0), 13 pancreas ca SIR 1.4 (0.7-2.4)	Because of industry coding cannot separate dry cleaners & laun-derers. Short latency for those who began work close to 1970 (duration employment unknown)
Travier et al. 2002 [Travier, et al. 2002]	IARC	Linkage census-cancer registry	>500,000 PYAR	Cancer diagnosis	Working in dry cleaning-laundry industry or as launderer-dry clearner or presser in 1960 and/or 1970, diagnosed 1971-89	Stratified by presumed start date based on age: if 60+ in 1960, C tet, Stoddard, TCE; <40 in 1960, PCE & C tet; 40-60, all four	Stoddard solvent, C tet, TCE	RR (vs non dry cleaners launderers) adj for age, era, region, urban/nonurbal) if in both censuses 389 ca RR 0.99 (0.9-1.1), 4 Hodgkins disease RR 2.7 (1.0-7.2), 15 leukemia RR 1.8 (1.1-3.1)	Industry & job coding could not separate dry cleaners, launderers. Short latency for any who began work close to 1970 (duration employment unknown)
Blair et al. 2003 [Blair, et al. 2003]	US NCI	Retro-spective cohort	5,369	Cause of death	Joined dry-cleaning union 1948-1978, VS to 1993	Exp score based on literature: operators 40; pressers, etc. 7; drop shops 0	Not reported	590 ca SMR 1.2 (1.1-1.3), 12 bladder ca SMR 1.3 (0.7-2.4), 27 cervix ca SMR 1.6 (1.0-2.3), 26 esophageal ca SMR 2.2 (1.5-3.3), 21 emphysema SMR 1.7 (1.0-2.5)	No strong relationship with duration or estimated solvent exposure

Reference	Study support/ affiliation	Study design	N	Outcome studied	Eligibility criteria	Exposure level	Other solvents, other exposures	Outcomes, ratio† (CI)	Study design issues
Boice et al. 1999 [Boice, et al. 1999]	Lockheed Martin Corporation	Retro-spective cohort	45.323 factory workers, 32,642 non-factory workers	Cause of death	Aircraft mfg ≥1 year >1959, 2267 exp to PCE VS to 1996	13% factory wkrs exp PCE	TCE primary degreaser to 1966, many other solvents, cutting fluids, asbestos, chromate	PCE exposed: 476 deaths SMR 0.90 (0.8-0.98), 141 ca SMR 1.07 (0.9-1.3), no ca COD SMR significantly up or down *RR non factory workers overall 0.9/0.76=1.18, all ca 1.07/0.8=1.34*	Multiple exp. Short latency for 11% factory , 24% non-factory workers who started after 1980. What about those employed 1928-1960?
Ruder et al. 2001, Ludwig et al. 1983 [Ludwig, et al. 1983; Ruder, et al. 2001]	NIOSH	Retro-spective cohort	1,708, incl 625 exp only to PCE	Cause of death	Member of dry-cleaning union, ≥1 y PCE exp <1960, no C tet	1977-79 level PCE: operators GM 22 ppm, pressers GM 3.3 ppm, counter workers 3.1 ppm.	1,083 exp "other" solvent, probably Stoddard solvent	271 ca SMR 1.3 (1.1-1.4), 10 bladder ca SMR 2.2 (1.1-4.1), 12 cervical ca SMR 2.0 (1.0-3.4), 14 esophageal ca SMR 2.5 (1.4-4.1), 82 respiratory disease SMR 1.3 (1.0-1.6)	No increase in liver or hematopoietic ca, bladder, esophageal increase by duration employment, latency

† Odds ratio OR, relative risk RR, standardized mortality ratio SMR, standardized incidence ratio SIR, 95% confidence interval ( ); The 95% confidence intervals (CI) are presented where reported (where not reported CIs were calculated, if possible).

* 90% confidence interval. *Calculations done for this paper are in italics*

Chemical abbreviations: Me Cl (methylene chloride). PCB (polychlorinated biphenyls), PCE (tetrachloroethylene), TCA (trichloroacetic acid--TCE metabolite), TCE (trichloroethylene), TCP (2,4,6-trichlorophenol)

Disease abbreviations: ca (cancer), dx (diagnosed), NHL (non-Hodgkins lymphoma), RCC (renal cell carcinoma)

Miscellaneous abbreviations: cum (cumulative), environ (environment, environmental), EPA (Environmental Protection Agency), est (estimated), exp (exposure, exposed), IH (industrial hygienist), JEM (job-exposure matrix), med (medical, medicine), Natl (National), NCI (National Cancer Institute), NIOSH (National Institute for Occupational Safety and Health), occup (occupational) TWA (time-weighted average), US (United States)

Statistical abbreviations: DFE (date 1st exposed), freq (frequency), F/U (followup), GM (geometric mean), IDR (incidence density ratio, chance of preganancy), mon (month), NSS (not statistically significant), p (probability), VS (vital status), y (year)