Trichloroethylene (TCE)

Jane Caldwell PhD, Ruth Lunn DrPH, and Avima Ruder PhD

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Current evaluation
Conclusion from the previous Monograph: Trichloroethylene (TCE) is *probably carcinogenic to humans (Group 2A)* based on limited evidence in humans for the carcinogenicity of TCE and sufficient evidence in experimental animals for the carcinogenicity of TCE. In making the overall evaluation, the Working Group considered the following evidence: (i) although the hypothesis linking the formation of mouse liver tumors with peroxisome proliferation is plausible, trichloroethylene also induced tumors at other sites in mice and rats. (ii) several epidemiological studies showed elevated risks for cancer of the liver and biliary tract and for non-Hodgkin lymphoma (NHL).

Exposure and biomonitoring
TCE is a volatile compound with moderate water solubility. Most TCE produced today is used for metal degreasing, in a number of industries (Bakke et al., 2007). The highest environmental releases are to the air. Ambient air monitoring data suggests that levels have remained fairly constant since 1999 at about 0.3 μg/m^3. Indoor levels are commonly 3 or more times higher than outdoors due to releases from building materials and consumer products. TCE is one of the most common groundwater contaminants and the median level based on a large study by the U.S. Geological Survey for 1985-2001 is 0.15 μg/L (USGS, 2006). It has also been detected in a wide variety of foods in the 1-100 μg/kg range. None of the environmental sampling has been done using statistically based national surveys. However, a substantial amount of air and groundwater data has been collected allowing reasonably well supported estimates of typical daily intakes by the general U.S. population: inhalation - 13 μg/day and water ingestion - 0.2 μg/day. The limited food data suggests an intake of about 5 μg/day, but this must be considered preliminary (U.S. EPA, 2009a)

High exposures have occurred to various occupational groups. Bakke et al. (2007) reviewed occupational exposure to TCE and reported that the arithmetic mean (AM) of the measurements across all industries and decades was 38.2 ppm. The highest personal and area air levels were reported in vapor degreasing (AM of 44.6 ppm). Past studies of aircraft workers have shown short-term peak exposures in the hundreds of ppm (>500,000 μg/m^3) and long-term exposures in the low tens of ppm (>50,000 μg/m^3). Occupational exposures have likely decreased in recent years due to better release controls and improvements in worker protection. However, some of that protection relies on personal protective equipment, not always consistently used, rather than engineering controls.

Exposure to a variety of TCE-related compounds, which include metabolites of TCE and other parent compounds that produce similar metabolites, can alter or enhance TCE metabolism and toxicity by generating higher internal metabolite concentrations than would result from TCE exposure by itself. Available estimates suggest that exposures to most of these TCE-related compounds are comparable to or greater than that to TCE itself.

Cancer in humans

(limited, vol 63, 1995)

Since the 1995 IARC review, there has been a plethora of publications evaluating TCE exposure and cancer in humans, including new cohort studies, updates of cohorts, case-control studies, review articles, and meta-analyses. Table 2 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)]. Three reviews have summarized most of the recent literature (Ruder, 2006; Scott and Chiu, 2006; Wartenberg et al., 2000). Many of the new studies have more sophisticated exposure assessment and thus allow for more accurate classification of TCE exposed workers (Scott and Chiu, 2006).

Meta-analyses can be useful for evaluating risks for rare or uncommon cancers. Wartenberg et al. (2000) conducted a comprehensive review of over 80 studies and evaluated the evidence for over 20 cancer sites. The review categorized the cohort studies into tiers based on the quality of the exposure assessments. Average risks (separate for incidence and mortality) were calculated for multiple cancer sites for each tier as well as for the case-control studies. In addition, meta-analyses have been published for liver cancer (Alexander et al., 2007), pancreatic cancer (Ojajärvi et al., 2001), NHL (Mandel et al., 2007), and multiple myeloma and leukemia (Alexander et al., 2006). However, there are limitations in these meta-analyses. Scott and Chiu (2006) updated the literature since the Wartenberg et al. review for kidney, liver and NHL.

Overall, the body of literature provides convincing evidence of a causal association between TCE exposure in humans and site-specific cancers, particularly in the kidney. Wartenberg et al. (2000) found a significant increased incidence of kidney cancer among cohorts with the best exposure assessments. Since the latest IARC review, five case-control studies of renal cell carcinoma have been published, all reporting elevated adjusted odds ratios for estimated TCE exposure (from non-statistically significant to >3.00) (Brüning et al., 2003; Charbotel et al., 2006; Dosemeci et al., 1999; Pesch et al., 2000; Vamvakas et al., 1998). In addition, two high-quality cohort studies of TCE exposed workers have also found an excess of renal cancer (Rasschou-Nielsen et al., 2003; Zhao et al., 2005). Risks increased with employment duration (Rasschou-Nielsen et al., 2003), exposure score (Zhao et al., 2005) or cumulative exposure (Charbotel et al., 2006). However, no association between TCE exposure and kidney cancer was found in the update of the Rocketdyne study (Boice et al., 2006).

Associations were also observed for NHL and liver cancer. Since the last review, four case-control studies generally reported excess relative risk estimates for NHL (Hardell et al., 1994; Persson and Fredrikson, 1999; Wang et al., 2009; Seidler et al., 2007), the relative risks

increased with increasing TCE exposure in two studies (Wang et al., 2009; Seidler et al., 2007). Increased risks were also found in two cohort studies (Hansen et al., 2001; Rasschou-Nielsen et al., 2003), and a significant increased risk (summary relative risk estimates [SRRE] = 1.59, 95% CI = 1.21 to 2.08) among TCE subcohorts in the highest quality studies was found in the meta-analysis (Mandel et al., 2006). No increased risk was found in an Italian case-control study (Costantini et al., 2008).

For liver cancer, the evidence is more limited mainly because only cohort studies are available and most of these studies have multiple solvent and other exposures as well as small numbers of cases due the comparative rarity of liver cancer (Scott and Chiu, 2006). While high quality studies reported generally excess relative risk estimates, they were generally based on small numbers of cases or deaths, resulting in wide confidence intervals on the estimates. The low number of liver cancer cases in the available studies made assessing exposure-response relationships difficult. Significant increased risks across high-quality studies were reported by Wartenberg et al. (2000) (for incidence cohort studies) and Alexander et al. (2007) (SSRE, 1.41, 95% CI = 1.06 to 1.87). Associations have also been reported for cancer at other sites, including urothelial, bladder and esophageal cancer (Ruder, 2006; Scott and Chiu, 2006).

Recent studies have found also found statistically significant associations between high TCE exposure and breast cancer (Sung et al., 2007), and prostate cancer (Krishnadasan et al., 2007). Radican and colleagues updated the Hill Air Force Base study using a job-exposure matrix for TCE exposure and saw no statistically significant elevated hazard ratios (Radican et al., 2008).

Molecular epidemiology studies

There is limited information on genetic susceptibility and cancer risk from TCE exposure, which is a major research gap. Wiesenhütter et al. (2007) reported that there was no difference in the distribution of glutathione *S*-transferase (*GST)* polymorphisms (*GSTT1*, *GSTM1*, *GSTP1*), and N-acetyltransferase (*NAT2*) genotypes (slow and rapid acetylators) among TCE-exposed cases, TCE-exposed controls, non-exposed cases and non-exposed controls using subjects from the renal cell case-control study conducted by Brüning et al. (1997a). However, the authors were not able to conduct analyses at the individual level due to legal constraints.

Cancer in experimental animals

(sufficient, vol 63, 1995)

TCE exposures in animals have been associated with effects in a number of targets that are relevant to human cancer targets as well. The central nervous system, the kidney, the liver, the immune system, the male reproductive system, and the developing fetus have been identified through epidemiological and experimental animal studies with more limited evidence for TCE toxicity to the respiratory tract and female reproductive system (U.S. EPA, 2001, U.S. EPA 2009a).

There are several other lines of supporting evidence for TCE carcinogenicity in humans. Multiple chronic bioassays in rats and mice have reported increased incidences of tumors with TCE treatment, including tumors in the kidney, liver, and lymphoid tissues – target tissues of

TCE carcinogenicity also seen in epidemiological studies. Of particular note is the site-concordant finding of low, but biologically and sometimes statistically significant, increases in the incidence of kidney tumors in multiple strains of rats treated with TCE by either inhalation or corn oil gavage (Maltoni et al., 1988; NTP, 1988; 1990). The increased incidences were greater in male rats than female rats, though, notably, pooled incidences in females from five rat strains tested by National Toxicology Program (NTP, 1988; 1990) results in a statistically significant trend (U.S. EPA, 2001, U.S. EPA 2009a).

With respect to the liver, TCE and its oxidative metabolites chloral hydrate (CH), trichloroacetic acid (TCA), and dichloroacetic acid (DCA) are clearly carcinogenic in mice, with strain and sex differences in potency that appear to parallel, qualitatively, differences in background tumor incidence (NCI, 1976; Maltoni et al., 1986; Anna et al., 1994; Herren-Freund et al., 1987; Bull et al., 2002; George et al., 2000; Leakey et al., 2003; Bull et al., 1990; DeAngelo et al., 1996; 1999; 2008). Data in other laboratory animal species are limited. Except for DCA, which has been reported to be carcinogenic in rats (Richmond et al., 1995; DeAngelo et al., 1996), inadequate evidence exists to evaluate the hepatocarcinogenicity of these compounds in rats or hamsters but TCE is clearly less potent in the strains of rats tested than in mice. Evidence for TCE-induced lymphatic cancers in rats and mice, lung tumors in mice, and testicular tumors in rats (Henschler et al., 1980; NTP, 1990; Maltoni et al., 1986; 1988; NTP, 1988; Fukuda et al., 1983) is more limited (U.S. EPA. 2009a).

With respect to the lymphatic cancers, two studies in mice reported increased incidences of lymphomas in females of two different strains, and two studies in rats reported leukemia in males of one strain and females of another. These tumors had relatively modest increases in incidence with treatment, and were not reported to be increased in other studies. Rodent bioassays have demonstrated a statistically significant increase in pulmonary tumors in mice following chronic inhalation exposure to TCE, and non-statistically significant increases in mice exposed orally. Pulmonary tumors were not reported in other species tested (i.e., rats and hamsters). Increased testicular (interstitial or Leydig cell) tumors have been observed in multiple studies of rats exposed by inhalation and gavage. Therefore, TCE 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). However, these studies show carcinogenic effects across different strains, sexes, and routes of exposure, and site-concordance with humans.

Mechanisms of carcinogenicity

Since 1995, a large body of literature has been published, on epidemiologic studies of TCE, various meta-analyses and criteria to proceed with appropriate meta-analyses, and studies describing the actions of TCE metabolites. During the course of development of the U.S. Environmental Protection Agency (EPA) draft TCE assessment, EPA's Scientific Advisory Board and the National Academy of Sciences (NAS) have provided insights regarding the large database with inferences about its carcinogenic hazard. EPA staff have published a mini-monograph outlining some of the outstanding science issues to be addressed in an assessment of TCE (Chiu et al., 2006a,b: Keshava and Caldwell, 2006; Scott and Chiu, 2006) as well as a number of subsequent publications (e.g., Caldwell et al., 2008; Guyton et al.,

2009; Evans et al., 2009) on its potential modes of action. Ruder (2006) provides an assessment of the epidemiological literature as stated above. In general, the following areas have seen large increases in the database and greater understanding of TCEs carcinogenic risk to humans.

Available mechanistic data do not suggest a lack of human carcinogenic hazard from TCE exposure.

1) The understanding of the toxicokinetics of glutathione conjugation (GSH) metabolites and conjugation pathways in humans has been deepened. Physiologically based pharmacokinetic (PBPK) models have been developed that allow for predictions of metabolism and differences in metabolism between species for a number of key metabolites (Chiu et al., 2006b; 2009; Evans et al., 2009).
2) Genotoxicity studies have included investigations of mutations of the Von Hippel-Lindau (*VHL)* gene in renal tumors of TCE exposed workers. Metabolism of *S*-dichlorovinyl-L-cysteine (DCVC), a mutagenic metabolite that transports to the kidney, lends biological plausibility to kidney cancer associated with human exposure. The documentation of increases in enzyme levels in the kidneys of humans exposed to TCE also lends plausibility to the kidney as a target of TCE toxicity and carcinogenicity in humans; the increases were observed (in non-cancer studies) at exposure levels that occur in occupational settings.
3) The epidemiological data (see above) identify other potential cancer sites and clearer signals with the addition of more studies since the previous IARC assessment. There is site concordance for multiple tumor types in both humans and experimental rodent studies that was not recognized previously.
4) The mode of action (MOA) of peroxisome-proliferation activated receptor (PPAR) activation, previously considered to dismiss the human relevance of effects observed in laboratory animals, has been questioned (e.g., Caldwell et al., 2008; Melnick et al., 2001) and the review by Guyton et al. (2009) of this proposed MOA raise questions about whether the hypothesized PPARα activation is either necessary or sufficient for rodent hepatocarcinogenesis (see DEHP review).
5) There is additional information regarding the toxicity of metabolites of TCE with multiple metabolites shown on their own to induce a carcinogenic response in rodent by potentially multiple MOAs (Caldwell et al., 2008). However, the MOA(s) has not been established for a number of TCE-induced tumors.

Toxicokinetics

TCE attains high concentrations relative to blood in the brain, kidney, and liver - all of which are important target organs of toxicity. TCE is cleared via metabolism mainly in three organs: the kidney, liver, and lungs. The metabolism of TCE is an important determinant of its toxicity. Metabolites are thought to be responsible for toxicity at multiple sites, particularly in the liver and kidney. Initially, TCE may be oxidized via cytochrome P450 (*CYP*) isoforms or conjugated with glutathione by *GST* enzymes. There are conflicting data as to which *GST* isoforms are responsible for TCE conjugation, with one study in rats indicating α*GST*s and another (also in rats) indicating μ and π*GST*. The balance between oxidative and conjugative metabolites generally favors the oxidative pathway, especially at lower concentrations, and

inhibition of *CYP*-dependent oxidation *in vitro* increases GSH conjugation in renal preparations. However, in humans, direct comparison of in vitro rates of oxidation and conjugation, as well as *in vivo* data on the amount of the TCE GSH conjugation to dichlorovinyl glutathione in blood, support a flux through the GSH pathway that may be much greater than that inferred from excretion of GSH-conjugation-derived urinary mercapturates (Chiu et al., 2006).

TCE carcinogenicity in humans is supported by toxicokinetic data indicating that TCE absorption, distribution, metabolism, and excretion are qualitatively similar in humans and rodents. Several metabolites and excretion products from both pathways have been detected in blood and urine from exposed humans as well as from at least one rodent species. Therefore, humans possess the metabolic pathways that produce the TCE metabolites thought to be involved in the induction of rat kidney and mouse liver tumors, and internal target tissues of both humans and rodents experience a similar mix of TCE and metabolites.

Quantitative interspecies differences in toxicokinetics do exist, and are addressed through PBPK modeling. Importantly, these quantitative differences affect only interspecies extrapolations of carcinogenic potency, and do not affect inferences as to the carcinogenic hazard for TCE. Recently, EPA and the U.S. Air Force jointly sponsored an integration of the Fisher, Clewell, and Bois modeling efforts (Hack et al., 2006). Different efforts have been published (e.g., Evans et al., 2009; Chiu et al., 2009; 2007; 2006; Hack et al., 2006) for PBPK model analyses or empirical analyses of toxicokinetics of TCE and its metabolites in mice, rats, and humans. Such analyses have considered a wider range of physiological, chemical, *in vitro*, and *in vivo* data than any previously published analysis of TCE. PBPK analysis should support high confidence in the model predictions and should provide appropriate characterization of the uncertainty in metabolic pathways for which available data were sparse or relatively indirect, such as GSH conjugation and respiratory tract metabolism. Key conclusions from the model predictions should include: (1) the extent of TCE metabolism at doses below saturation, and (2) GSH conjugation and subsequent bioactivation in humans and its relation to previous estimates. The predictions of the PBPK model could then be used in inter- and intraspecies extrapolation of toxicokinetics.

Genotoxicity and VHL Mutation

For the kidney, there is now a predominance of positive genotoxicity data for TCE metabolites derived from GSH conjugation (in particular DCVC). Together with toxicokinetic data, these data are consistent with their systemic delivery to and in situ formation in the kidney.

Studies have been conducted to determine the role of *VHL* gene mutations in TCE-induced renal cell carcinoma. Renal-cell carcinomas from workers occupationally exposed to high levels of TCE had a higher frequency of overall VLH mutations, and C to T transitions than renal cell-carcinomas from non-TCE exposed people (Brüning et al., 1997b; Brauch et al., 1999; 2004). Because of their limitation or lower mutation detection rate, the two other available studies (Schraml et al., 1999; Charbotel et al., 2007) neither add nor detract to the conclusions from the earlier studies. Inactivation of the *VHL* gene through mutations, loss of heterozygosity and imprinting has been observed in about 70% of renal clear cell carcinomas

(Alimov et al., 2000; Kenck et al., 1996). However, while supporting the biological plausibility of mutagenesis as a MOA for TCE-induced kidney tumors, available data on the *VHL* gene in humans or transgenic animals do not conclusively elucidate the role of *VHL* mutation in TCE-induced renal carcinogenesis.

Modes of Action:

Cytotoxicity and compensatory cell proliferation, presumed to be mediated through metabolites formed after GSH-conjugation of TCE, have also been suggested to play a role in the MOA for renal carcinogenesis. Human studies have reported markers for nephrotoxicity at current occupational exposures but data are lacking at lower exposures. Nephrotoxicity alone appears to be insufficient, or at least not rate-limiting, for rodent renal carcinogenesis as toxicity has been observed in both mice and rats at high doses but kidney tumors only observed in rats and nephrotoxicity has not been shown to be necessary for kidney tumor induction by TCE in rodents. It is not clear if nephrotoxicity is one of several key events in a MOA or TCE-induced kidney cancer or is a marker for an "upstream" key event that may contribute independently to both nephrotoxicity and renal carcinogenesis, or if it is incidental to kidney tumor induction. As no data suggest that any of the proposed key events for TCE-induced kidney tumors rats are precluded in humans, TCE-induced rat kidney tumors provide additional support for the human evidence of TCE-induced kidney cancer.

Data are insufficient to conclude that any of the other hypothesized MOAs are operant for other TCE-induced tumor sites. In the liver, there is evidence for genotoxic effects mediated through CH (e.g., micronuclei induction following exposure to CH is positive in most test systems in both i*n vitro* and *in vivo* assays, and most recently in humans (Ikbal et al., 2004)), or some other oxidative metabolite of TCE. The previous IARC evaluation considered the MOA hypothesis for TCE-induced liver tumors involving activation of the PPARα receptor. Clearly, *in vivo* administration of TCE leads to activation of PPARα in rodents and likely does so in humans as well. However, the evidence as a whole does, rather than support PPAR-α activation as the sole operant MOA mediating TCE hepatocarcinogenesis, support multiple TCE metabolites and multiple toxicity pathways contributing to TCE-induced liver tumors (Caldwell et al., 2008).

Furthermore, recent experiments have demonstrated that PPAR-α activation and the sequence of key events in the hypothesized MOA are not sufficient to induce hepatocarcinogenesis and that the events comprising the hypothesized MOA are not necessary for liver tumor induction (Guyton et al*.,* 2009; see DEHP review for further discussion of the PPAR- α MOA). For mouse lung tumors, a mutagenic MOA involving CH has also been hypothesized, but there are insufficient data to conclude that it is operant. A second MOA hypothesis for mouse lung tumors that involve cytotoxicity and regenerative cell proliferation has only limited experimental support with no data on proposed key events in experiments of duration 2 weeks or longer. A MOA involving *in situ* oxidative metabolism, whether leading to mutagenicity, cytotoxicity, or other key events, may also be relevant to other tissues where TCE would undergo P450 metabolism. For the testes, *CYP2E1*, oxidative metabolites, and protein adducts have been reported after TCE exposure and this has been identified as a tumor target in rodents. However, inadequate data exist to adequately define a MOA hypothesis for this tumor site.

Research needs and recommendations:

Human cancer studies

Pooled or Meta-analysis: The NAS stated that there were weaknesses in the available meta-analyses. As outlined by Scott and Chiu (2006) meta-analyses of high-quality studies should be able to determine if estimated relative risks or odds ratios in cohort and case-control studies are consistent, robust, and insensitive to individual study inclusion, with no indication of publication bias or significant heterogeneity. A meta-analyses approach is warranted given the modest relative risk estimates and the relative rarity of the cancers observed, and therefore the limited statistical power of individual studies. Pooled analyses of the biomonitoring studies (measuring TCA metabolites) (Anttila et al., 1995; Axelson et al., 1994; Hansen et al., 2001) should also be explored.

Primary studies: Any planned cohort studies should endeavor to obtain, at a minimum, current and retrospective department-specific measured exposure levels of TCE and other exposure agents. A cohort without multiple solvent exposures, such as the manufacture of kitchen utensils, using TCE for a final degreasing after assembly-line production, would be desirable. Scott and Chiu (2006) noted that known inaccuracies exist between cancer incidence and death certificate recording for some of the cancer sites that have been associated with TCE exposure such as liver and biliary cancer and NHL. Studies evaluating cancer incidence rather than mortality are desirable especially when looking at NHL. Scott and Chiu (2006) noted that evaluation of lymphomas and TCE exposure is complicated by (1) the use of different ICD codes in the different studies (ICD codes for lymphomas have changed over time, and different studies have used different ICD revisions and (2) understanding of the biology of NHL has changed; lymphomas can be either B cell or T cell and thus lymphomas in the past may have been diagnosed as multiple myeloma or leukemia. If possible medical records or data on molecular markers of lymphoma should be obtained to provide more information on the diagnosis of lymphohematopoietic cancers. Studies evaluating liver cancer should look for possible interaction with lifestyle factors.

Genetic susceptibility: 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 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* and other *CYP* genes, as well as any other genes coding for enzymes that metabolize TCE or its metabolites, should also be investigated. Other candidate genes for genetic susceptibility includes those involve in regulating immune function. Studies should also be conducted using entire genome scans to identify new susceptibility genes.

Mechanistic considerations

Research is needed to determine whether there are specific metabolites that appear to be the agent of carcinogenesis for specific sites. The multiple MOAs from multiple metabolites make comparisons between chlorinated solvents difficult to study and can account for differences in exposures and pharmacokinetic and pharmacodynamic characteristics of exposed populations contributing to variable responses in a number of studies. Information is needed on pathway effects, especially epigenetic changes induced by TCE and its metabolites, Research is needed to determine whether the effects on particular pathways be key to the lack

of site concordance for some endpoints between animals and human data for TCE (e.g., a particular pathway disturbance will manifest as susceptibility to differing tumor sites between species). Studies evaluating epigenetic changes induced by TCE and its metabolites are also useful for determining potential MOAs involved with TCE-induced effects.

Immunologic mechanism may be involved in lymphomagenesis from solvents (Vineis et al., 2007) and this should also be an area of future research.

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TABLE 2. Studies (published since 1995 IARC review) Evaluating Trichloroethylene Exposure and Cancer Risk (Ruder 2006)

Reference	Study support/ affiliation	Study design	N	Outcome studied	Eligibility criteria	Exposure level	Other solvents, other exposures	Outcomes, ratio† (CI)	Study design issues
Brüning et al. 2003	Deutsch For-schungs-geimein-schaft, US EPA	Case-control, hospital-based	134 cases, 401 controls	Renal cell cancer diagnosis	Case: nephrectomy 1992-2000 ; control: hospitalized 1999-2000 (no dementia, no cancer)	High exposure = narcosis during TCE job	PCE, C tet, other solvents, heavy metals, fuels, paints, welding, etc.	Longest job in industry with TCE exposure, OR 1.8 (1.0-3.2); any "metal degreasing" OR 5.6 (2.3-13.3); est high TCE exp OR 3.7 (1.8-7.5) (all smoking adjusted)	OR decreased with increasing duration of TCE or solvent exposure
Charbotel et al. 2006, Fevotte et al. 2006	European Chlorinated Solvents Association	Case-control, hospital-based	86 cases, 316 controls	RCC diagnosis	Case: dx 1993-2003; controls same MD (no urinary tract cancer, chronic kidney disease), matched to case on gender, birthyear $\pm$ 2	Expert assessment of occupational history	Other solvents, oils, welding fumes, lead, cadmium, asbestos	High cum dose TCE OR 2.16 (1.02-4.60); high dose + peaks OR 2.73 (1.06-7.07); excluding jobs with low confidence scores, high cum dose OR 3.34 (1.27-8.74); high dose + peaks OR 3.80 (1.27-11.4)	Hospital/urologi st patient controls
Costantini et al. 2008, Miligi et al. 2006	US NCI, Europe Against Cancer Programme, Italian Alliance Against Cancer	Case-control, populatio n 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 TCE exposure as very low-low (LO) or medium-high (HI)	Benzene, styrene, xylene, toluene, dichlorome-thane, tetra-chloroethylene. 1,1,1-trichloro-ethane	AML LO OR 1.0 (0.4-2.5), HI OR 1.1 (0.5-2.9); CLL LO OR 1.2 (0.5-.7), HI OR 0.9 (0.3-2.6); MM LO OR 1.5 (0.7-3.5), HI OR 0.9-2.4); NHL LO OR 0.8 (0.5-1.3), HI OR 1.2 (0.7-2.0)	Leukemia & MM ORs for higher doses were lower, possible latency/lag issues, no solvent specific results presented for HL
Dosemeci et al. 1999	US NCI	Case-control	438 cases, 687 controls	RCC diagnosis	RCC dx July 1988-1990, population-based controls	Industry, job linked to JEM	Other chlorinated solvents	Any/none OR adj age, gender, smoking, hyper-tension, diuretics, BMI: all 1.30 (0.9-1.9), men 1.04 (0.6-1.7), women 1.96 (1.0-4.0)	Gives % exp but not number exp. Est 57 cases 69 controls exp. Multiple exp

Reference	Study support/ affiliation	Study design	N	Outcome studied	Eligibility criteria	Exposure level	Other solvents, other exposures	Outcomes, ratio† (CI)	Study design issues
Dumas et al. 2000, Siemiatycki et al. 1991	Québec Institute Research Occup Health Safety & Health Research Funds; Canada Health, Natl Health Research & Develop-ment, NCI	Case-case (different sites) and case-control	3730 cancer patients, 533 population controls	Cancer diagnosis	Males age 35-70, dx 9/79-6/85, resident in Montreal metropolitan area on electoral list	Low, medium, high intensity & no, low, med, high frequency assigned by coders; reanalysis (rectal cancer only 257 cases) adjusts for other exposures	Many	Rectal ca: any exp OR 2.0 (1.0-3.9) substantial exp OR 0.9 (0.3-3.2), melanoma any exp OR 2.6 (1.3-5.0), substantial OR 2.3 (0.9-5.8)	Multiple exp. Low number with any/high exp (12/3 rectal ca cases, 8/4 melanoma)
Greenland et al. 1994	U. Lowell Research Foundation General Electric Corpora-tion	Case-control nested in cohort	1821 deceased workers	Cause of death	Employed <1985, died 1969-1984 age 21-90, death reported to pension office, work history available, controls nonca, nonblood, nondigestive, nonmental, nongenito-urinary causes	JEM created for TCE & 6 other exposures	PCB, benzene, other solvents, machine fluids, astestos, resins	Any TCE: pancreas ca OR 1.64 (0.8-3.3), liver & biliary ca OR 0.54 (0.1-2.6), other sites ORs closer to 1 (NSS).	Work histories not available for 34% of deceased workers Multiple exp
Hardell et al. 1994	Umea Hospital (?)	Case-control	105 NHL cases, 335 population-based controls	NHL	Cases dx 1974-1978 age 25-85, controls matched for sex, age, residence, vital status	Occupational history, self-reported exposures	Phenoxyacetic acids, chlorophenols, bezine, turpentine, white spirit, degreaser	TCE OR 7.2 (1.3-42) based on 4 exposed cases & 4 exp controls	Almost all substances show statistically significant elevated OR but no occupations do
Heineman et al. 1994, Gomez et al. 1994	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. 41% estimated exp. to TCE/	JEMs also for other chlorinated solvents	Low cum exp OR adj age, location 0.9 (0.5-1.6), med adj OR 1.3 (0.8-2.2), high adj OR 1.3 (0.7-2.5), test for trend not statistically significant	Interviewed <50% (300/ 741 cases, 320/ 741 controls). Low number with medium or high exp (50 cases, 40 controls)

Reference	Study support/ affiliation	Study design	N	Outcome studied	Eligibility criteria	Exposure level	Other solvents, other exposures	Outcomes, ratio† (CI)	Study design issues
Krishnadasan et al. 2007	California Cancer Research Program	Nested case-control	362 cases, 1,805 controls	Prostate cancer	Employed 1950-1993 at Rocketdyne. Cases: ID by link to 8 cancer registries, Controls matched 5:1 on age at 1st employment ± 2, age at case dx ± 2	JEM created from company records, walk-throughs, interviews	PAHs, hydrazine, benzene, other solvents	Low moderate TCE OR 1.3 (0.81-2.1), high TCE OR 2.1 (1.2-3.9), P trend 0.02	Multiple exposures, some controls could have been dx with prostate ca before registries started
Nordstrom et al. 1998	Swedish Work Environment Fund, Orebro County Council	Case-control	121 male hairy cell leukemia cases, 484 population-based controls	Hairy cell leukemia	Cases diagnosed 1987-1993; controls matched 4:1 for age and county	Exposure assessed from occupational & lifestyle questionnaire	Numerous exposures	TCE OR 1.5 (0.7-2.6), 9 exposed cases, 26 exposed controls	Only ever/never exposure? so no way to assess exposure-response
Persson and Fredrikson 1999		Case-control (2 studies)	(1) 106 NHL cases, (2) 93 NHL cases, 479 population based referents	NHL	Cases age 20-80, Swedish-born, alive, (1) dx 1964-1986, Orebro Med Ctr or (2) dx 1975-1984, Linkoping Hospital	Lifestyle and occupational questionnaire, exposure ≥1 year 5-45 years pre-dx	Other solvents, etc.	TCE OR 1.2 (0.5-2.4)	
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	TCE JEM ORs: Medium exp males 1.1 (0.9-1.4), females 1.2 (0.6-1.7); high males 1.1 (0.9-1.4), females 1.3 (0.8-2.0); substantial males 1.3 (0.9-1.8), females 0.8 (0.3-1.9). TCE JTEM ORs: Medium exp males 1.3 (1.0-1.8), females 1.3 (0.7-2.6); high males 1.1 (0.8-1.5), females 0.8 (0.4-1.9); substantial males 1.3 (0.8-2.1), females 1.8 (0.6-5.0)	Combined OR (both sexes) not presented, trend tests (med-high-substantial) not done

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. 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	TCEJEM ORs: Medium exp males 1.1 (0.8-1.3), females 1.0 (0.6-1.7); high males 1.1 (0.9-1.4), females 1.6 (1.0-2.5); substantial males 1.3 (0.9-1.7), females 0.6 (0.2-2.3). TCE JTEM male ORs: Medium exp 0.8 (0.6-1.2), high 1.3 (0.9-1.7), substantial 1.8 (1.2-2.7)	Combined OR (both sexes) not presented, trend tests (med-high-substantial) not done
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 $\pm$ 1 year	Complete occupa-tional history assigned intensity & frequency of TCE by case-status blinded industrial physician	PCE, carbon tet, dichloromethane, benzene, toluene, xylene, styrene	<4.4 ppm years adj OR 0.7 (0.4-1.1), 4.4-35 ppm years adj OR 0.7 (0.5-1.2), >35 ppm years adj OR 2.1 (1.0-4.8), trend p 0.14 B-cell NHL trend p 0.02	No exposure measurements. Mixed exposures?
Vamvakas et al. 1998	Institute Toxicology, U. Wurzburg, Germany	Case-control	58 cases, 84 controls	RCC	Cases dx Dec 1987-May 1992 in one hospital, controls hospitalized trauma 3 nearby hospitals 1993, had sonography to exclude kidney cancer	Occ history + TCE, PCE modules, exp ranked by time & freq, severity pre-narcotic symptoms	PCE, heavy medals, petro-leum products, benzene, asbestos, PCB, pesticides	19 cases & 5 controls exp (+2 controls exp PCE). Means in exp: duration exp cases 16$\pm$ 11.3 y, controls 8$\pm$7.7y (NSS); latency cases 33$\pm$ 10.4, controls 18$\pm$7.2, p<0.01 *Exp v. unexp* X^2*=5.36, p<0.025*	Interviewers not blinded, controls from different era & hospitals, younger than cases (p<0.05).
Wang et al. 2009	US NCI	Case-control	601 female NHL cases, 717 female population-based controls	NHL	Cases: dx 1996-2000 age 21-84, controls by random digit dialing or Medicare-Medicaid frequency matched by 5-year age groups	Structured questionnaire linked to job-expsoure matrix	Benzene, other chlorinated solvents	TCE ORs: ever/never 1.2 (0.9-1.8); intensity low 1.1 (0.8-1.6), med-high 2.2 (0.9-5.4), trend p 0.06; probability low 1.1 (0.7-1.8), med-high 1.4 (0.9-2.4), trend p 0.37	

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 #	Finnish Work Med Fund, US NIOSH grant	Linkage monitoring registry-cancer registry	1,698 men, 1,391 women	Cancer diagnosis	Monitored (urine) for exposure any time during 1965-1983; cancer diagnosed 1967-1992	Median 48 µmol TCA/L (men), 63 µmol TCA/L (women).	Small % also monitored for PCE, 1,1,1-trichloroethane	Overall: 208 ca SIR 1.1 (0.9-1.2), 8 cervix ca SIR 2.4 (1.1-4.8), 8 NHL SIR 1.8 (0.8-3.6). 20+ ys since 1st exp: 60 ca SIR 1.6 (1.2-2.0), 7 stomach ca SIR 3.0 (1.2-6.1), 3 liver ca SIR 6.1 (1.3-17.7), 8 prostate ca SIR 3.6 (1.5-7.0), 7 lymph-ohematopoietic SIR 3.0 (1.2-6.1)	74% only 1-2 measurements (short duration employment?) .
Hansen et al. 2001	Interna-tional Epi-demiology Institute	Linkage monitor-ing registry-cancer registry	803 workers	Cancer diagnosis	Monitored (urine) for exposure any time during 1947-1989; cancer diagnosed 1968-1996	Median 25 µg TCA/ ml (1947-64), 2 µg TCA/ ml (1980-89), overall 15 µg TCA/ ml (1947-89)	Not reported	Overall: 128 ca SIR 1.0 (0.9-1.2), 4 cervix ca SIR 3.8 (1.0-9.8), 8 NHL SIR 3.1 (1.3-6.3), 6 leukemia SIR 2.0 (0.7-4.6), 5 liver SIR 2.1 (0.7-5.2).	No data provided on ca risk by duration of employment
Axelson et al. 1994#	Occup Environ Med, U. Hospital, Linkoping, Sweden	Retro-spective cohort	1421 men, 249 women	Cause of death, cancer dx	Wked at 1 of 115 companies where urinary TCA monitored 1955-1975, F/U from 1st urine not DFE, VS to 1986	Mean TCA <50/µg/ ml urine for 80%, ~ TWA 20 ppm	Not reported	Men 229 deaths SMR 0.97 (0.9-1.1), 37 ca SMR 0.65 (0.5-0.9), 138 circulatory SMR 1.17 (1.0-1.4), 107 ca dx SIR 0.96 (0.8-1.2), 8 skin ca SIR 2.36 (1.0-4.7). Women 24 deaths SMR 1.55 (1.0-2.3), 10 ca SMR 1.53 (0.7-2.8), 10 circulatory SMR 2.02 (0.97-3.7), 22 ca dx SIR 1.32 (0.9-2.0). No dose-response gradients.	Incomplete cohort minus nonmonitored workers (n=?)

Reference	Study support/ affiliation	Study design	N	Outcome studied	Eligibility criteria	Exposure level	Other solvents, other exposures	Outcomes, ratio† (CI)	Study design issues
Blair et al. 1998, Stewart et al. 1991	US NCI	Retro-spective cohort mortality & cancer incidence	14,457 workers, 7,282 ever exposed to TCE	Death/ cancer diagnosis	Civilian aircraft maintenance workers s employed >1 y between 1952-956 at Hill AFB, VS to 1990, ca incidence 1973-1990	Job-exposure matrix, quantified for TCE, tertiles of <5, 5-25, >25 unit-ys	other chlori-nated solvents All but 3,739 workers exp 1-25 chemicals	TCE/no chemicals: all death RR adj age, calendar time, sex 1.0, all ca RR 1.1 (1.0-1.3). Ca incidence in men: Colon RR 4.1, 1.4-11.8 (nonTCE chem/none); 2.9, 1.0-8.9 (<5 TCE/ none); 4.3, 1.4-13 (5-25 TCE/none); 5.7, 2.0-16.7 (>25 TCE/ (nonTCE chem/none); 1.2, 0.1-14 (<5 TCE/none); 1.0, 0.1-16 (5-25 TCE/none); 2.6, 0.3-25 (>25 TCE/ none). Multiple myeloma RR 3.7, 0.4-32 (non-TCE chem/none); 0.8, 0.1-12.7 (<5 TCE/none); 3.8, 0.4-37 (5-25 TCE/none); 5.1, 0.6-44 (>25 TCE/ none).none). Liver RR 0.8, 0.1-12	Mixed exposures. Evaluation by job title, not person
Radican et al. 2008	US NCI	Retro-spective cohort mortality & cancer incidence	14,457 workers, 7,282 ever exposed to TCE	Death/ cancer diagnosis	Civilian aircraft maintenance workers s employed >1 y between 1952-956 at Hill AFB, VS to 2000, ca incidence 1973-1990	Job-exposure matrix, quantified for TCE, tertiles of <5, 5-25, >25 unit-ys, TCE exposure categories: LI (low intermittent), LC (low continuous), PI (peak infrequent), PF (peak frequent)	other chlori-nated solvents All but 3,739 workers exp 1-25 chemicals	4320 deaths HR 1.04 (0.98-1.09), cancer 854 deaths HR 1.03 (0.91-1.17), no COD in SS excess	Mixed exposures. Evaluation by job title, not person

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	Lockheed Martin Corporation	Retrospective cohort	45.323 factory workers, 32,642 non-factory workers	Cause of death	Aircraft mfg ≥1 year >1959, 2267 exposed to TCE VS to 1996	TCE primary degreaser to 1966 (12% factory wkrs exp	PCE from 1966, many other solvents, cutting fluids, asbestos, chromate	TCE exp: 1110 deaths SMR 0.83 (0.8-0.9), 277 ca SMR 0.86 (0.8-0.97), 7 pancreas ca SMR 0.41 (0.2-0.9), 78 lung ca SMR 0.76 (0.6-0.95), no other ca SMR significantly up/down *RR TCE exp/non-factory workers overall 0.83/ 0.76=1.09, all ca 0.86/ 0.8=1.08*	Multiple exp. Short latency for 11% factory , 24% non-factory workers who started after 1980. What about those employed 1928-1960?
Boice et al. 2006	Boeing Corporation	Retrospective cohort	41,351 Rocketdyne workers, 8372 Santa Susana Field Lab, 32,979 elsewhere	Cause of death	Rocket engine testing ≥6 mo 1948-1999, VS to 1999	TCE	Hydrazines, fuels, propellants, oxidizers, other solvents	SSFL 2251 deaths, SMR 0.83 (0.80-0.86), cancer 655 deaths, SMR 0.89 (0.82-0.96), kidney cancer 21 deaths, SMR 1.15 (0.71-1.76)	No latency for those recently employed, 4729 current (SSFL, 613) employees contribute PYAR but not deaths
Henschler et al. 1995 #	Toxicology Institute, U. Wurzburg, Germany	Retrospective cohort	169 men exp TCE, 190 men unexp	RCC incidence, mortality	Cardboard workers exp ≥1 y 1956-75, VS to 1992	TCE predominant solvent 1956-75	Pentachlorophenol, 1,1,1-trichloroethane, aromatic & chlorinated solvents	Exp 50 deaths SMR 0.68 (0.5-0.9), 15 ca SMR 0.96 (0.5-1.7), 2 kidney ca SMR 3.28 (0.4-11.8). Unexp 52 deaths SMR 1.03 (0.8-1.4), 15 ca SMR 1.16 (0.7-1.9), 3 brain ca SMR 9.38 (1.9-27.4) Exp 5 renal ca dx SIR 7.97 (2.6-18.6), unexp no renal ca.	

Reference	Study support/ affiliation	Study design	N	Outcome studied	Eligibility criteria	Exposure level	Other solvents, other exposures	Outcomes, ratio† (CI)	Study design issues
Morgan et al. 1998	Hughes Aircraft Company	Retro-spective cohort	4,733 TCE exp, 15,975 unexp	Cause of death	Wked ≥6 mo 1950-1985 in aerospace mfg, VS to 1993	Degreasers (high) >50 ppm. JEM rated low (1), medium (4), high (9) exp, cum=mon x score	Not reported	All deaths 917 TCE SMR 0.84 (0.8-0.9), 3135 nonTCE SMR 0.85 (0.8-0.9); ca 270 TCE SMR 0.92 (0.8-1.0), 830 nonTCE SMR 0.85 (0.8-0.9); ovarian ca 8 TCE SMR 1.21 (0.5-2.4), 5 nonTCE SMR 0.39 (0.1-0.97); prostate ca 21 TCE SMR 1.18 (0.7-1.8), 55 nonTCE SMR 0.86 (0.7-1.1); kidney ca 8 TCE SMR 1.32 (0.6-2.6), 24 nonTCE SMR 1.10 (0.7-1.6) ; bladder ca 8 TCE SMR 1.36 (0.6-2.7), 15 nonTCE SMR 0.70 (0.4-1.2) *RR TCE/nonTCE: all deaths 1, all ca 1.08, ovarian ca 3.10, prostate ca 1.37, kidney ca 1.2, bladder ca 1.94*	Probably have multiple exp
Raaschou-Nielsen et al. 2003	Internat-ional Epi-demiology Institute	Retro-spective cohort	40,049 incl 14,360 higher exp	Cancer diagnosis	347 TCE-using companies, <200 employees in company, blue-collar jobs, worked ≥3 mons 1964-1997.	Higher exp: worked ≥1 y, started <1980	Not reported. Main industries metal, elec-tronics, painting, printing, chemical, dry cleaning	All ca men SIR 1.1 (1.0-1.1), women SIR 1.2 (1.0-1.3); RCC 1.2 (0.9-1.5); NHL 1.2 (1.0-1.5); esophageal SIR 1.8 (1.2-2.7). Higher exp RCC 1.4 (1.0-1.8); NHL 1.5 (1.2-2.0); esophageal SIR 1.7 (0.9-2.9).	RCC & NHL risk increased with increasing duration of employment, higher among higher exp
Ritz 1999	US NIOSH grant	Retro-spective cohort	3814	Cause of death	White males hired 1951-72, wked ≥3 mon U processing plant, monitored for radiation, VS to 1990	JEM for no, low, med TCE exposure x duration	Uranium, cutting fluids, kerosene	Exp >5 yrs med TCE v. no TCE, 15 yr lag : liver ca RR 12.1 (1.0-144), brain ca RR 14.4 (1.2-167) adj radiation, salary v. hourly, latency	Multiple exp

Reference	Study support/ affiliation	Study design	N	Outcome studied	Eligibility criteria	Exposure level	Other solvents, other exposures	Outcomes, ratio† (CI)	Study design issues
Sung et al. 2007	Taiwan Dept. of Health, National Health Research Institutes	Retro-spective cohort	63,982 female workers	Breast cancer incidence	Employed ≥1 day at electronics factory 1973-1992, dx 1979-2001 (could have been employed starting in 1970?)	Duration of employment <June 1974 (TCE only) & later (15 other solvents)	Isopropyl alcohol, acetone, MEK, trichlorometh-ane, methylene chloride, toluene, petrol-eum naphta, N-hexane, ethyl acetate, methyl alcohol, 1,2-dichloroethylene, 1,1,1- & 1,1,2-trichloro-ethane, 1,2-dichlorethane, tetrachloroethylen e	Pre 1974 employment SIRs: <1 mo, 1.97 (0.98-3.52); 1-11 mo 1.22 (0.73-1.90), 1-4 years 1.38 (1.81-2.22), 5-9 years 1.14 (0.70-1.76), >10 years 1.62 (1.02-2.42), overall 1.38 (1.11-1.70) Post 1974 employment SIR overall 0.99 (0.85-1.14)	How could workers have pre 1974 employment of >4 years?
Zhao et al. 2005	California Cancer Research Program(?)	Retro-spective cohort	55,000 workers	Cancer incidence and mortality	Employed 1950-1993 at Rocketdyne, matched to National Death Index, cancer registries of California, Arizona, Arkansas, Florida, Nebraska, Nevada, Oregon, Texas, and Washington State	Industrial hygiene review of facility, job description manuals, no-low-med-high exposure assigned by job title	Hydrazine, mineral oils	Incidence: Kidney cancer, med TCE RR 1.87 (0.56-6.20), high RR 4.90 (1.23-19.6), trend p 0.02; bladder cancer, med TCE RR 1.54 (0.81-2.92), high RR 1.98 (0.93-4.22), trend p 0.07	

† 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*

Study included in the 1999 IARC review

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-Hodgkin 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)

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IARC Technical Publication No. 42

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Views and Expert opinions of an IARC/NORA expert group meeting

Lyon, France: 30 June – 2 July 2009

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