Carcinogenicity of trichloroethylene, tetrachloroethylene, some other chlorinated solvents, and their metabolites

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In October, 2012, 18 experts from seven countries reassessed the carcinogenicity of several chlorinated solvents and some of their metabolites at the International Agency for Research on Cancer (IARC), Lyon, France (table). These assessments will be published as volume 106 of the IARC Monographs.[2]

Trichloroethylene (TCE) was widely used for degreasing metal parts until the 1990s, and in dry cleaning from the 1930s to 1950s. It is still used for stain removal, but its main use is in chlorinated chemical production. An estimated 276 000 workers in the European Union were exposed to TCE in the early 1990s,[3] although occupational exposure levels are decreasing.[4] The general population is exposed through consumer products—including food—and contaminated water.

The Working Group classified TCE as carcinogenic to humans (Group 1). Biotransformation of TCE, well characterised in humans and animals, occurs primarily through oxidative metabolism by cytochrome P450 enzymes and also via glutathione conjugation by glutathione S-transferase enzymes. The main oxidative metabolites are dichloroacetic acid (DCA), trichloroacetic acid (TCA), and chloral hydrate (CH). Metabolites of TCE formed via glutathione conjugation are genotoxic, particularly in kidney cells in which in-situ metabolism occurs.

Case-control studies provide convincing evidence for a positive association between exposure to TCE and renal-cell carcinoma. Two studies[5,6] have evaluated confounding for several kidney cancer risk factors, and provided evidence of an exposure–response relationship. A French study,[5] done in an area with high prevalence of occupational exposure to TCE, reported an odds ratio (OR) of 2·16 (95% CI 1·02–4·60) for people with high cumulative exposure after adjusting for smoking and body-mass index, and 1·96 (0·71–5·37) when also adjusted for exposure to cutting fluids and other petroleum oils. An eastern European study[6] was larger than the French study but had lower exposure prevalence. The OR was 1·63 (95% CI 1·04–2·54) for any exposure to TCE and 2·34 (1·05–5·21) in the highest category of exposure intensity.[6] Consistent with the importance of glutathione conjugation for kidney carcinogenesis, TCE-exposed people with an active GSTT1 enzyme had an increased risk (OR 1·88, 95% CI 1·06–3·33), but people without GSTT1 activity did not (0·93, 0·35–2·44).[6]

Cohort studies of aircraft and aerospace workers in the USA and a Danish study of workers in industries using TCE have reported modestly increased relative risks (RRs) of kidney cancer, with indications of an exposure–response relationship.[7–9] Three small, independent cohorts of Nordic workers who were monitored biologically by TCA in urine show little evidence of an increased risk of kidney cancer. However, level of exposure varied widely and few measurements per worker were available.

A meta-analysis[10] also reported significant RRs of kidney cancer; 1·3 overall and 1·6 for high-exposure groups. Confounding by smoking is unlikely to account for the increased risk of kidney cancer, since RRs for lung cancer were not increased in most cohorts or in the meta-analysis. Furthermore, case-control studies generally adjusted for smoking and other potential confounders, with little effect on risk estimates.

The epidemiological evidence for the association between TCE exposure and non-Hodgkin lymphoma (NHL) or liver cancer was limited. The cohort studies, including the biologically monitored Nordic cohorts, and several case-control studies reported slightly increased risks of NHL, with weak indication of an exposure–response relationship. Several genotoxic and non-genotoxic TCE-induced

	Uses and exposures	Evidence for carcinogenicity in humans	Evidence for carcinogenicity in animals	Group*
Trichloroethylene	Chemical intermediate; metal degreasing	Sufficient	Sufficient	1
Tetrachloroethylene	Dry cleaning solvent; metal degreasing; chemical intermediate	Limited	Sufficient	2A
1,1,1,2-tetrachloroethane	Solvent in pesticides, cleaning, degreasing, and extracting processes; chemical intermediate for chlorinated solvents	Inadequate	Sufficient	2B
1,1,2,2-tetrachloroethane	Solvent; metal degreasing; chemical intermediate for chlorinated solvents	Inadequate	Sufficient	2B
Dichloroacetic acid	Water disinfection byproduct; cauterising and therapeutic agent; chemical intermediate	Inadequate	Sufficient	2B
Trichloroacetic acid	Water disinfection byproduct; herbicide; treatment for skin conditions; urinary biomarker of exposure to trichloroethylene and other chlorinated solvents	Inadequate	Sufficient	2B
Chloral and chloral hydrate†	Sedative; water disinfection byproduct	Inadequate	Sufficient	2A

*See IARC preamble[1] for explanation of classification system. †Exist in equilibrium in aqueous solution.

***Table*: Agents assessed by the Monograph 106 Working Group**

mechanisms could contribute to liver carcinogenesis, and alterations of immune response in people and animals might lead to haematological cancers.

TCE is a multisite carcinogen in mice and rats of both sexes by both oral and inhalation exposure: increased incidence of tumours of the liver, kidney, lung, testes, and haemopoietic system occurred in several studies.

Tetrachloroethylene is one of the most widely used chlorinated solvents. From the 1950s to 1980s, its main use was in dry cleaning, for which it is still widely used. Tetrachloroethylene was also used in metal degreasing, but its current primary use is for chlorofluorocarbon production. Present sources of exposure for the general population are dry cleaning and environmental contamination (through air and drinking water).

Epidemiological studies noted positive associations between tetrachloroethylene exposure and several cancers, including bladder, oesophagus, kidney, cervix, and NHL; however, there was a consistent pattern across studies only for bladder cancer. The Working Group focused its assessment on studies that specifically assessed exposure to tetrachloroethylene or work in dry cleaning. The largest cohort studies were of dry cleaners in four Nordic countries[11] and in the USA.[12,13] None of these studies controlled for smoking; however, the Nordic study used unexposed laundry workers as the comparison group to indirectly control for tobacco and alcohol consumption. All three cohorts had an increased risk of bladder cancer. The Nordic study reported a significantly increased incidence, which is a better measure than mortality in view of the low case-fatality. None of the cohort studies reported notable exposure–response relationship, except one[13] (standardised mortality ratio 4·08, 95% CI 2·13–7·12; among workers exposed for more than 5 years and first exposed more than 20 years previously). Several case-control studies of bladder cancer, including all those assessing dry cleaners, showed positive associations after adjustment for smoking and other potential confounders. The Working Group classified the epidemiological evidence as limited because employment in dry cleaning was the only indicator of exposure to tetrachloroethylene in most studies, the number of exposed cases was small, and the exposure–response relationship was weak.

Tetrachloroethylene is also metabolised via cytochrome P450-mediated oxidation and glutathione conjugation. TCA is the predominant metabolite. Findings from cancer bioassays in mice and toxicity studies in animals have identified several potential genotoxic and non-genotoxic mechanisms of carcinogenesis for tetrachloroethylene in the liver that could operate in people. In rats, tetrachloroethylene induces neoplasms of the haemopoietic system, testes, kidney, and brain. No mechanistic data exist to inform the bladder cancer findings in people. Tetrachloroethylene was classified as probably carcinogenic to humans (Group 2A).

CH is used as a sedative and is also a byproduct of water disinfection. The only case-control study of cancer incidence in patients given CH was uninformative. Sufficient evidence exists of carcinogenicity in animals; several studies of mice showed an increased incidence of hepatocellular adenomas and carcinomas. CH was upgraded to Group 2A, on the basis of its genotoxicity in most experimental systems and in humans; notably, a study of infants given CH as a sedative showed increased micronucleus formation.[14]

Several chronic bioassays in mice show that DCA, TCA, 1,1,1,2-tetrachloroethane, and 1,1,2,2-tetrachloroethane increased the incidence of hepatocellular tumours. These agents were classified as possibly carcinogenic to humans (Group 2B) on the basis of sufficient evidence for carcinogenicity in animals.

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We declare that we have no conflicts of interest.

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PHD has worked and consulted for a trade association (Halogenated Solvents Industry Alliance) representing producers of trichloroethylene and perchloroethylene, and has invested in a mutual fund that includes shares in chemical companies. GS has represented the European Chlorinated Solvents Association. All other Working Group members, specialists, representatives, and secretariat declare that they have no conflicts of interest.