



IARC MONOGRAPHS



TRICHLOROETHYLENE, TETRACHLOROETHYLENE, AND SOME OTHER CHLORINATED AGENTS

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IARC MONOGRAPHS
ON THE EVALUATION
OF CARCINOGENIC RISKS
TO HUMANS

GENERAL REMARKS

This one-hundred-and-sixth volume of the *IARC Monographs* evaluated the evidence for carcinogenicity of seven chlorinated solvents, including trichloroethylene, tetrachloroethylene, and their metabolites (dichloroacetic acid, trichloroacetic acid, and chloral hydrate). These solvents share metabolic pathways and have anaesthetic properties via their effects on the central nervous system. All the agents listed here were evaluated previously by the *IARC Monographs* programme ([IARC, 1979, 1986, 1987, 1995, 1999a, 2004](#)). In light of new epidemiological and mechanistic evidence published since the previous evaluation published in 1995, the Advisory Group to the *IARC Monographs* in 2008 recommended the re-evaluation of trichloroethylene and other chlorinated solvents ([IARC, 2008](#)). A summary of the findings of this Volume has appeared in *The Lancet Oncology* ([Guha et al., 2012](#)).

Trichloroethylene

Trichloroethylene is a chlorinated solvent that has been produced commercially since the 1920s. Trichloroethylene was previously used as an anaesthetic, a stain-remover in dry-cleaning, an ingredient in paints, adhesives, cleaners, and more recently, for degreasing metal parts and as a feedstock for producing chlorinated chemicals. Although occupational exposure was once widespread due to the myriad uses for trichloroethylene, exposure levels and the number of exposed workers in Europe and North America have declined by at least one order of magnitude since the 1940s. Some of the heaviest exposures have occurred in workers in industries involving the manufacture and repair of aircraft and automobiles, and in screw-cutting.

Trichloroethylene has been found in outdoor and indoor air, water, soil, food, and animal tissues, and exposure from environmental

sources (including hazardous-waste sites and contaminated water) is common in the USA and elsewhere throughout the world.

Trichloroethylene was evaluated previously by the *IARC Monographs* (Volumes 20, 63, and supplement 7; [IARC, 1979, 1987, 1995](#)). In 1995, the Working Group classified trichloroethylene as *probably carcinogenic to humans (Group 2A)* based on sufficient evidence for carcinogenicity in experimental animals and limited evidence in humans. The epidemiological assessments at that time were largely driven by observations of an elevated risk of cancer of the liver and biliary tract and non-Hodgkin lymphoma ([IARC, 1995](#)).

The re-evaluation of trichloroethylene by IARC in 2012 resulted in a new classification in Group 1, *carcinogenic to humans*, based on sufficient epidemiological evidence for cancer of the kidney, with strong mechanistic support from studies in experimental animals and exposed humans. The epidemiological data also

identified limited evidence for an association with liver cancer and non-Hodgkin lymphoma. The Working Group also noted that the data for trichloroethylene are very informative with regard to demonstrating tumour-site concordance between humans and experimental animals; several rare cancers were observed in animals in the absence of common “background” tumours.

Tetrachloroethylene

Tetrachloroethylene is one of the most important chlorinated solvents worldwide. Used today in dry-cleaning and as a feedstock for the synthesis of fluorocarbons, applications in the past included degreasing metals and the production of chlorofluorocarbons. Occupational exposure has been, and continues to be, widespread. Despite considerable reduction in exposure resulting from technological advances in dry-cleaning and degreasing in the USA and in Europe, high-exposure situations continue to exist in some countries. Individuals living or working in the vicinity of dry-cleaning shops are also exposed, and exposure from environmental sources (including hazardous-waste sites and contaminated water) is common. Tetrachloroethylene has been detected in indoor and outdoor air, water, food and in animal and human tissues.

Tetrachloroethylene was evaluated previously by the *IARC Monographs* (Volumes 20, 63, and supplement 7; [IARC, 1979, 1987, 1995](#)). In 1995, the Working Group classified tetrachloroethylene as probably carcinogenic to humans (Group 2A), based on sufficient evidence in experimental animals and limited evidence in humans for cancers of the oesophagus and cervix and non-Hodgkin lymphoma ([IARC, 1979, 1987, 1995](#)). This classification was maintained in the re-evaluation of tetrachloroethylene by the Working Group in 2012 and was based on

sufficient evidence in experimental animals and limited evidence in humans for an excess of cancer of the urinary bladder in dry-cleaning workers. The urinary bladder was a new tumour site identified from the epidemiological data; the Working Group noted the paucity of supporting evidence from mechanistic data. A systematic review and meta-analysis describing the evaluation of tetrachloroethylene by the Working Group, focusing on studies of dry-cleaning workers, has been prepared ([Vlaanderen et al., 2014](#)).

The Working Group decided against presenting a separate *Monograph* on dry-cleaning workers, as was done previously (Volume 63; [IARC, 1995](#)). This is consistent with the strategy of the IARC Monographs programme to evaluate specific agents, rather than mixtures or occupations, whenever possible. The primary rationale supporting the focus on specific agents in this case was the improved exposure assessment available for trichloroethylene and tetrachloroethylene in epidemiological studies addressing their carcinogenic effects. In addition, a more diverse array of dry-cleaning agents has come into use, and the frequency and intensity of exposure to trichloroethylene and tetrachloroethylene in dry-cleaning workers have decreased drastically in the last decades, in regions where epidemiological studies have been performed.

Chloral hydrate

Chloral hydrate is a metabolite of trichloroethylene and is also a by-product of chlorine-based water disinfection. It has been used as a hypnotic drug since the 1870s, and was once widely used for sedating children before dental, medical, or diagnostic procedures. Although still in use, it has largely been replaced by newer drugs with a lower potential for overdose. Chloral hydrate was previously classified in Group 3 by the Working

Group in 1995 and 2004 ([IARC, 1995, 2004](#)). In 2012, the Working Group re-classified chloral hydrate in Group 2A based on sufficient evidence of carcinogenicity in animals and strong evidence for genotoxicity (DNA damage) in mammalian and other test systems, both *in vivo* and *in vitro*. The Working Group considered noteworthy one study in infants exposed orally to chloral hydrate, which reported a significant increase in micronucleus formation in peripheral blood lymphocytes ([Ikbal et al., 2004](#)). The only available epidemiological study was uninformative as to the relationship between exposure to chloral hydrate and risk of cancer in humans. Thus the mechanistic data were crucial for characterizing the carcinogenic hazard in the absence of epidemiological data.

Other evaluations

Three of the remaining compounds – trichloroacetic acid ([IARC, 1995, 2004](#)), 1,1,1,2-tetrachlorethane and 1,1,2,2-tetrachlorethane ([IARC, 1999b](#)) – were previously classified in Group 3. In 2012, the Working Group classified these compounds as *possibly carcinogenic to humans* (Group 2B) based on *sufficient* evidence in experimental animals. The Working Group also affirmed the classification of dichloroacetic acid in Group 2B ([IARC, 2004](#)). Supporting evidence included cancer bioassays demonstrating increased incidence of hepatocellular tumours in mice.

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