OCCUPATIONAL EXPOSURE OF TRICHLOROETHYLENE: TOXICITY, CURRENT STANDARDS AND SUGGESTED NEW BIOMARKERS FOR KIDNEY CANCER

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(Received: 3 September 2019 ; Revised: 30 October 2019 ; Accepted: 21 November 2019)

Abstract

Trichloroethylene (TCE) is a well-known volatile organic compound. The chemical is widely used as a solvent for degreasing metal or electronic parts in industries. For years, the potential health risk associated with occupational exposure to TCE has been constantly studied. It has been known that the primary routes of TCE exposure are chemical inhalation and dermal absorption. The health effects are related to the period of exposure and the concentration. Short-term exposure to TCE may affect the nervous system, liver, kidneys and immune system, while long-term exposure has been linked to carcinogenic tumors in several target organs such as liver and kidneys. For the occupational exposure standpoint, the regulations and recommendations generated by U.S. federal government agencies were explained in this article. The mechanisms of action when TCE was absorbed into the body were also elaborated in detail. It was found that TCE can be metabolized into two different pathways: oxidation and conjugation. Each pathway has different target organs. For example, the oxidative pathway can mainly affect the liver, whereas the glutathione (GSH) conjugation goes to kidneys. For both acute and chronic effects, dose-response relationships were identified in this article. Thus, the objective of this article is to update the current situation and to review the toxicity of TCE with epidemiology data, especially kidney-related cancer, for better understanding.

Keywords: Trichloroethylene, Chemical exposure, Carcinogen, Occupational health, Workplace

INTRODUCTION

This article is intended to profoundly review the toxicology, mechanisms of action, and epidemiology proof in the extent of carcinogenicity of trichloroethylene (TCE). TCE or C_2HCl_3, is a colorless liquid with chloroform–like odor (Todd et al., 2019). This organic chemical is usually known as a volatile chlorinated hydrocarbon compound. There are several common names such as acetylene trichloride, 1–chloro–2,2–dichloroethylene and ethylene trichloride (Dodge & Goodman, 2015; Hudson & Dotson, 2017). TCE has been used in industries since 1920 (Green, 2004). In the past, TCE was utilized as general anesthetic, vanishes, lacquers, paints and adhesive (Dodge & Goodman, 2015). Nowadays, TCE is being used as a component for generating another chemical as well as a solvent to degrease the equipment because of its lipophilic property for metal–working, dry cleaning, textile manufacturing and painting industries. For instance, TCE was utilized to clean the surface metal parts in a clock manufacturing factory, Thailand (Singthong et al., 2015).

BASIC TOXICOLOGY

The primary exposure routes of TCE are inhalation and dermal absorption (Dodge & Goodman, 2015; Forkert et al., 1985; Green, 2004; Todd et al., 2019). The principle effects of TCE exposure can affect the liver, kidneys, reproductive system, central nervous system and fetus development (Al–Griw et al., 2015; Chiu et al., 2012; Fan et al., 2014; Forkert et al., 1985; Loch–Caruso et al., 2019). The fundamental toxicology of TCE consists of acute and chronic effects (Gilbert et al., 2016; Zamanian et al., 2019).

The acute effect is dependent upon the concentration and routes of exposure. Symptoms such as headache, dizziness and fatigue can be noticed when the TCE is inhaled at approximately 200 ppm (Dodge & Goodman, 2015; Kishi et al., 1993). The depth perception and movement are disabled at the exposure of 1000 ppm (Dodge & Goodman, 2015). Also, there have been reports that TCE can cause dermatitis or skin irritation (Chittasobhaktra et al., 1997; Kim & Rho, 2014; Todd et al., 2019). In addition, a study showed that high levels of TCE circulated in blood is corresponded to high levels of depression in the central nervous system (Kishi et al., 1993).

Chronic exposure of TCE is usually presented in terms of cancer. Several studies have shown that repeated exposure to TCE can cause many types of cancers such as liver

and kidney cancer (Bakke et al., 2007; Brüning & Bolt, 2000; Hansen et al., 2013; Herman et al., 1994; Todd et al., 2019). The onset kidney toxicity is usually detected when the exposure to TCE occurs for almost 20 years (Moore et al., 2010). United States Environmental Protection Agency (USEPA) (2011) also provided the cancer assessment for TCE exposure. The oral slope factor for carcinogenic risk is 4.6×10^{-2} per mg/kg–day, which was extrapolated from physiological based pharmacokinetic (PBPK) model studies collaborating with kidney cancer, non–Hodgkin's lymphoma (NHL) and liver cancer (USEPA, 2011). The inhalation unit risk for carcinogen is 4.1×10^{-6} per g/m^3, which was derived from linear extrapolation at low dose of TCE in animal studies (USEPA, 2011).

Moreover, according to the health hazard assessment for TCE exposure effects other than cancer, the reference dose (RfD) for oral exposure at 5×10^{-4} mg/kg–day can provide several adverse effects such as cardiovascular, immunological and developmental functions in animals (USEPA, 2011). For example, the cardiovascular effect was studied on the number of fatal cardiac malformation in Sprague–Dawley rats from TCE exposure through drinking water (Johnson et al., 2003). On the other hand, the reference concentration (RfC) for inhalation exposure was determined at 0.002 mg/m^3 with similar observed health effects compared to the RfD.

MECHANISMS OF ACTION

This part is written to explain the toxicokinetic of TCE when it is absorbed into the body. TCE can be metabolized into two different pathways including oxidation by cytochrome P450 enzymes and glutathione (GSH) conjugation (Dodge & Goodman, 2015; Kim et al., 2009; Lash et al., 2006; Moore et al., 2010, 2011). It has been showed that the liver effects are usually resulted from oxidative TCE metabolized, while the kidney effects are influenced from TCE metabolized in GSH conjugation pathway (Figure 1) (Chiu et al., 2012; Dodge & Goodman, 2015).

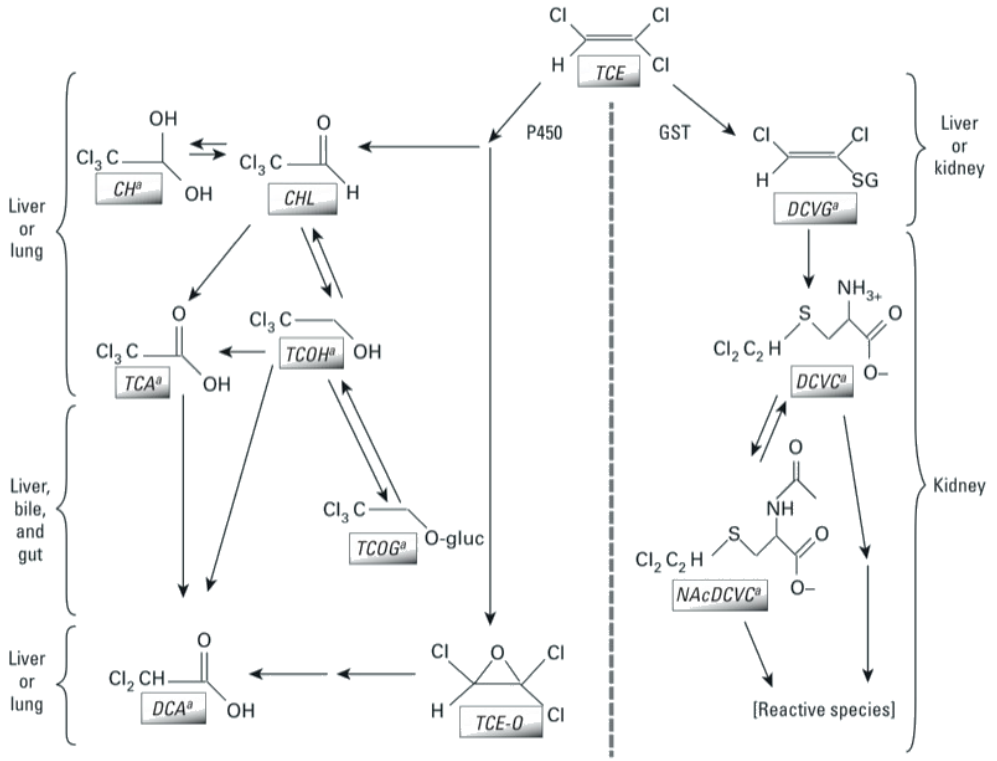

Figure 1 Metabolism of TCE through two main pathways: oxidation; left, conjugation; right. Reprinted from "Human Health Effects of Trichloroethylene: Key Findings and Scientific Issues," by Chiu, W. A., Jinot, J., Scott, C. S., Makris, S. L., Cooper, G. S., Dzubow, R. C., ... Caldwell, J. C, 2012, **Environmental Health Perspectives,** 121(2), 303–311. Copyright (2013) by the US Department of Health and Human Services.

The metabolites generated by the oxidative pathway are dichloroacetic acid (DCA), chloral hydrate and trichloroacetic acid (TCA) (Figure 1) (Chiu et al., 2012; Dodge & Goodman, 2015). These metabolites are created in relatively lower amount compared to another pathway (Lash et al., 2006). The metabolites from the oxidative reaction are hepatotoxic, which could cause adverse effects to liver (Hansen et al., 2013; Vlaanderen et al., 2013).

On the other hand, GSH conjugation pathway can generate metabolites such as S–(1,2–dichlorovinyl) glutathione (DCVG) and N–acetyl–S–(1,2–dichlorovinyl)–1–cysteine (NAcDCVC) (Figure 1) (Cummings et al., 2000; Kim et al., 2009; Lash et al., 2006). The major

metabolite in this pathway is DCVG. Usually, DCVG is either transferred to bile duct or circulated through plasma and then finally terminated at the kidneys. Recent studies showed that GSH conjugation is the main pathway causing kidney malfunction leading to renal cell carcinoma (RCC) (Cummings et al., 2000; Desimone et al., 2013; Moore et al., 2010; Yoo et al., 2015).

THE DEVELOPMENT OF RENAL CELL CARCINOMA

Kidney cancer or renal cell carcinoma (RCC) has been noticed that it is developed from mutation of a specific gene. Clear cell renal cell carcinoma (ccRCC) is the most usual subtype (70%) of RCC, which is related to the specific gene, the von Hippel–Lindau (*VHL*) tumor suppressor gene (Brüning, 1999; Herman et al., 1994). The occurrence of RCC is related to the inactivation of *VHL* gene (Moore et al., 2011; Niu et al., 2011). The *VHL* gene is basically responsible for oxygen concentration and stability of the hypoxia–inducible transcription factor family (HIFs) (Desimone et al., 2013). The primary inactivating mechanisms of *VHL* gene leading to ccRCC include missense mutation, deletion, and hyper–methylation (Niu et al., 2011). To be more specific, an alteration of the *VHL* protein from proline to serine at the 81^{th} codon (P81S) is considered as a major cause of renal carcinogen (approximately 40% of the TCE–exposed group) to develop ccRCC (Brauch et al., 1999). TCE–induced P81S VHL mutation is able to modify the cells' growth rate in order to survive the depressed environment such as hypoxia (Desimone et al., 2013). Therefore, the alteration in P81S *VHL* gene may lead to DNA damage, as a result of the irregular tumor growth in the cells.

As a result, TCE is suggested as a genotoxicity and mutagenicity chemical, especially in kidneys from GSH conjugation pathway (Lash et al., 2014). Exposure to TCE consequently enhances the possibility to alter the tumor suppressor (*VHL* gene) functions. The alteration of *VHL* could lead to HIF accumulation since the degradation system fail to function normally. Then, the excessive amount of HIF in renal cells could highly activate the metabolic reprogramming, which induces renal tumors in human (Desimone et al., 2013).

EPIDEMIOLOGICAL DATA

The epidemiological studies can be used to investigate the relationship between the TCE exposures and the adverse health effects in human. TCE is brought from occupational scale to population scale due to the broad extent of exposure. The public has been concerned of TCE contamination through environment. The hazardous waste and drinking water are the main sources of TCE for the public (Moore et al., 2010). According to an epidemiological study among central European population, there is a strong relationship between TCE exposure and risk of renal sarcoma with 1.63 odd ratio (Moore et al., 2010). Thus, the odds of having renal cancer is 1.63 higher among the TCE exposure group compared to the group with no exposure to TCE.

From 1998–2008, approximately 147 persons (18–21 years old) were reported of having adverse symptoms due to exposure to TCE (with 5 fatalities) (Sangchom, 2009). However, the epidemiological data collected in Thailand is limited. Hence, there is a need for additional epidemiological research in Thailand.

Another cohort study was conducted in area of Nordic countries, which included Finland, Sweden and Denmark. Totally, 5,553 workers who had TCE exposure were recruited into the research. The participants had been monitored for TCE exposure with TCA, an important metabolite and current biomarkers recommended by ACGIH (2019), in urine samples for 42 years from 1947 to 1989. The data demonstrated such a high incidence ratio between TCE exposure and liver cancer incidence (1.93; 95% CI = 1.19 to 2.95) (Hansen et al., 2013). On the other hand, the result for kidney cancer standardized incidence ratio was 1.01 (95% CI = 0.70 to 1.42). As you can see, the association ratio was close to 1, which means that there is quite low relationship between exposure to TCE and kidney cancer (Hansen et al., 2013). It can be concluded that the study might not strongly support that TCE can cause kidney cancer. However, at the 95^{th} percentile of the population, the ratio was 1.42, which is relatively solid enough to suggest that TCE exposure is likely associated with a risk of having kidney cancer (Hansen et al., 2013).

CARCINOGENIC DETERMINATION

Several organizations established their identification programs for carcinogenic evaluations. The carcinogen classifications of TCE from different organizations were listed below (Table 1).

Table 1 Summary of TCE classification for carcinogenicity by various organizations

Organization	Carcinogenic determination
NIOSH (2018)	Potential occupational carcinogen
U.S. EPA (2011)	Carcinogenic to humans
IARC (2014)	Group 1: Carcinogenic to humans
National Toxicology Program (NTP) (2016)	Known to be a human carcinogen
ACGIH (2019)	Group A2: Suspected human carcinogen

OCCUPATIONAL EXPOSURE LIMITS (OELs)

The standards for occupational exposure in different organizations of TCE were elaborated in this section (Table 2).

Table 2 Summary of OELs for TCE exposure established by different organizations

Organization	Time weighted average (8-hour)
OSHA	100 ppm
NIOSH	25 ppm*
ACGIH	10 ppm

*10-hour'

The occupational safety and health administration (OSHA) determined the permissible exposure limit (PEL) for TCE at 100 ppm 8-hour time weighted average (TWA) and the concentration must not exceed 200 ppm for the ceiling limit throughout the working period (the peak may reach 300 ppm at most 5 minutes in any 2 hours period) (OSHA, 2004).

The National Institute for Occupational Safety and Health (NIOSH) announced recommended exposure limit (REL) of 25 ppm (10-hour TWA) (NIOSH, 2018). In addition, the American Conference of Governmental Industrial Hygienists (ACGIH) also provides threshold limit values (TLV) for TCE at 10 ppm (TWA) and 25 ppm for short-term exposure

limit (STEL) with basic warnings to potential of central nervous system impairment, cognitive decrements and renal toxicity (ACGIH, 2019).

BIOMARKERS OF EARLY KIDNEY TOXICITY

For occupational biological exposure standpoint, the biomarkers recommended by ACGIH (2019) are trichloroacetic acid (TCA) in urine and trichloroethanol in blood. The biological exposure indices (BEIs) of these two biomarkers are 15 mg/L and 0.5 mg/L, respectively. Both BEIs are recommended to collect the samples at the end of shift at the end of workweek. Due to the potential health effects of being exposed to TCE, it is important to select a highly reliable and sensitive biological marker in order to detect early exposure. Additionally, the traditional biological markers mentioned above are usually used for assessing kidney function, but not for specifically representing actual kidney injury. It can be noted that they merely represent abnormal function of the kidneys such as creatinine and blood urea nitrogen.

Vermeulen et al. (2012) conducted a cross–sectional study in order to evaluate the kidney toxicity/function among 80 workers who were exposed to TCE from the workplace and compare to the non–exposed group. The exposure levels were analyzed from personal air sampling and urine sampling. The results demonstrated that there was a significantly difference between two groups of TCE exposure. The amount of detected kidney injury molecule–1 (KIM–1) in the exposed group (162.7 Geometric mean (GM) ± 2.19 Geometric Standard Deviation (GSD)) was significantly higher than the non–exposed group (254.1 GM ±1.87 (GSD)) ($P < 0.0001$) (Vermeulen et al., 2012). According to the biotransformation of TCE, the used biomarkers for nephrotoxicity used in this study were glutathione S transferase alpha type and pi type (Alpha–GST and Pi–GST) and KIM–1. It can be noticed that these biomarkers are able to detect the kidney toxicity at the early stage (Vermeulen et al., 2012). It is noted that KIM–1 represents a very sensitive marker of renal injury especially acute kidney injury. KIM–1 is known as a protein on epithelial cells of proximal tubules that moderate and engulf dead cells in surrounding area. It is normally released through the urine when the kidney cells are injured. Not only KIM–1 has higher sensitivity compared to other renal biomarkers, but KIM–1 protein also cannot be found in urine if a kidney functions normally, otherwise there is renal tubular injury (Vermeulen et al., 2012).

CONCLUSION

In the past, TCE was used in multiple purposes such as anesthetic, grain fumigant and wound disinfectant. However, these uses were gradually banned by the further studies in TCE exposure and hazards. However, TCE is still being used in some industries as a solvent and a degreasing agent. The data from experimental and epidemiological studies suggest that exposure to TCE is relatively related to cancer development. This article especially focused on exposure to TCE and renal cell carcinoma. Furthermore, the newly presented biological markers (KIM–1 and Alpha– or Pi–GST) were introduced for the future consideration.

It is expected that the workers who are at risk of exposure to TCE should be protected. The main protection should be corresponded to the routes of chemical exposure regardless of the exposed concentration due to its carcinogenicity. Engineering control is highly recommended. The examples of control should include local exhaust ventilation, general dilution ventilation, a process enclosure and the proper wear of appropriate personal protective equipment.

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