Chapter 3
Hypersensitivity Dermatitis and Hepatitis

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Abstract Occupational exposure to trichloroethylene (TCE) rarely induces severe generalized hypersensitivity dermatitis accompanying grave hepatitis, referred to as occupational TCE hypersensitivity syndrome (HS), in susceptible workers. TCE HS resembles delayed-type severe cutaneous adverse reactions to drugs and is totally different from solvent-induced irritating contact dermatitis. Importantly, human herpesvirus 6, which remains latent within the body after primary infection during infancy, is reactivated in most patients, and the reactivation affects the clinical course of this disease. Lines of evidence have established the current notion that TCE has sensitization potency. Though human leucocyte antigen (HLA)-B*13:01 has been identified as a marker of individual susceptibility, appropriate occupational hygiene practices to reduce the exposure and the biological monitoring of urinary TCE metabolites can be crucial to preventing this disease. Since the causal relationship between TCE exposure and this life-threatening occupational disease can be overlooked, the disease needs special attention from occupational health professionals and clinicians.

Keywords Trichloroethylene • Hypersensitivity • Dermatitis • Hepatitis • Human herpesvius 6 • Drug-induced hypersensitivity syndrome (DIHS) • HLA-B*13:01 • Urine • Trichloroacetic acid

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3.1 Occupational Trichloroethylene Hypersensitivity Syndrome: Hypersensitivity Dermatitis Due to Trichloroethylene Exposure

Trichloroethylene (TCE) (CAS number: 79-01-6) is still an important industrial solvent today, used for degreasing during production of metal parts. Although the production volume of TCE has been decreasing, especially in developed countries, health problems related to TCE exposure remain an important occupational health issue at least in some Asian countries since there are a large number of exposed workers. The annual production of TCE in China and Japan was 160,900 and 47,745 t in 2010, respectively.

In workshops where organic solvent is used, skin problems, mostly irritant contact dermatitis, are in general the frequently encountered occupational health issues. The dermatitis is primarily attributable to irritation due to the local defatting action of the solvent, in which skin surface lipids, the lipid material in the stratum corneum, and the fatty fraction of the cell membranes are dissolved (Wahlberg and Adams 1999). However, workers engaging in a job exposed to TCE could also suffer from idiosyncratic generalized dermatitis accompanying grave hepatitis, which is totally different from the irritant contact dermatitis (Huang et al. 2002; Kamijima et al. 2007). The mortality rate of this disease is surprisingly high, i.e., 9–13 %. Liver failure, infections, and the resulting sepsis are the principal causes of fatalities (Phoon et al. 1984; Pantucharoensri et al. 2004; Kamijima et al. 2007).

This generalized dermatitis resembles severe drug hypersensitivities, and is designated as occupational TCE hypersensitivity syndrome (HS). It is mediated by a delayed-type hypersensitivity mechanism, but is not classified as allergic contact dermatitis, which only involves the areas of skin directly contacting TCE liquid. It could involve whole body surface, even the mucous membrane in the oral cavity and genitalia. In addition to the characteristics of the rash, about a 1-month duration from the commencement of exposure to the disease onset, fever, abnormally increased leukocyte number, lymphadenopathy, liver dysfunction and the resulting fatalities, and the recurrence just after the minimal re-exposure overlap characteristics of a disease entity referred to as severe cutaneous adverse reactions to drugs, namely drug-induced hypersensitivity syndrome (DIHS) or drug reaction with eosinophilia and systemic symptoms (DRESS) (Huang et al. 2006; Watanabe et al. 2010; Watanabe 2011; Kamijima et al. 2013). Since TCE still plays a significant role as a degreasing solvent today and this life-threatening occupational disease can be misdiagnosed as generalized drug eruptions, the disease needs particular attention of occupational health professionals and clinicians.

3.2 Epidemiology of Trichloroethylene Hypersensitivity Syndrome

The incidence rate of TCE HS is by far lower than TCE-induced irritant contact dermatitis. Though the exact incidence rate of the disease remains unclear today, the disease prevalence estimated from previous reports ranges between 0.25 and 12.5 % (Kamijima et al. 2007), which suggests that the prevalence depends on exposure dose and the existence of one or more certain individual susceptibility factors. The first description of TCE HS can be found in an American textbook on occupational skin disorders that was published in 1947 as follows: "It (TCE) is also a sensitizer and can cause a more or less generalized acute eczematoid type of dermatitis which begins as an erythema, becomes papular, then vesicular, and is followed by oozing, crusting, and desquamation" (Schwartz et al. 1947). However, the authors did not mention the possibly accompanying hepatitis, fever, hematological abnormalities, lymphadenopathy and mucosal lesions, which are important features of this disease and will be described in more detail later in this chapter. After this publication, less than ten cases of TCE HS were reported in each decade between 1960 and 1990 from a limited number of industrialized countries, i.e., USA, Japan, Singapore and Spain (Bauer and Rabens 1974; Conde-Salazar et al. 1983; Phoon et al. 1984; Goh and Ng 1988; Nakayama et al. 1988; Hisanaga et al. 2002). In contrast, the reported number increased dramatically after the mid-1990s mainly in industrializing Asia, particularly in China where more than 300 cases have been reported (Huang et al. 2002; Dai et al. 2004; Kamijima et al. 2007). In China, patients were found in some provinces, but the number of reported cases was by far the largest in a southern part of China, Guangdong Province. This growing number of disease occurrences was considered to be partly attributable to the rapid economic development in that area and the resulting increase in the use of TCE and exposed populations (Huang et al. 2002), especially after the conclusion of the Montreal Protocol to phase out the use and production of chlorofluorocarbons and 1,1,1-trichloroethane. Patients were also reported in Korea, Singapore, Thailand, Philippines, USA, and Japan until this day (Bond 1996; Chittasobhaktra et al. 1997; Tan et al. 1997; Estrella-Gust et al. 1999; Goon et al. 2001; Pantucharoensri et al. 2004; Kamijima et al. 2007; Ikeoka et al. 2009; Watanabe et al. 2010; Jung et al. 2012). Those patients were mostly engaged in degreasing, especially cleaning metal-made products, machines, plastic toys, or electronics parts. Degreasing work using TCE thus seems to carry a higher risk of suffering from this disease.

It should be noted that an occupational history linked to TCE exposure can be overlooked in a patient exhibiting generalized rash if the clinician does not ask the patient questions focusing on solvent exposure (Watanabe et al. 2010). There may be more latent patients even in developed countries today. However, the number of

workers engaging in solvent-exposed work in factories is generally small in these countries, and poor working environments in terms of TCE exposure are encountered in small-scale enterprises rather than in large-scale ones. Given the very low incidence rate of TCE HS, workplace-based epidemiological studies to clarify the precise rate are practically difficult to carry out.

3.3 Characteristics and Pathophysiology of Trichloroethylene Hypersensitivity Syndrome

3.3.1 Clinical Features Common to Severe Cutaneous Adverse Reactions to Drugs

As mentioned in the introductory part of this review, TCE HS shows characteristics common to delayed-type severe drug hypersensitivities. The characteristics of the disease are summarized in Table 3.1. Duration of exposure is one of the most important features of this disease. The duration is 4 weeks on average, and almost all within 3 months. If a heavily-exposed worker does not suffer from the disease during this period, he/she is not susceptible. The initial symptom is fever (>38 °C) or rash, or both. The fever is often considered a sign of any infectious disease, and an antibiotic and/or an antipyretic can be prescribed, following which a generalized rash appears and possibly be misdiagnosed as drug eruption. Jaundice is often seen from the early stage of the clinical course (Kamijima et al. 2007).

The dermatitis starts as a diffuse erythematous maculopapular rash on the extremities, face, neck or trunk, and spreads to the entire body surface within one to several days. Chinese researchers in the field of occupational and clinical medicine, focusing on the rash's similarity to generalized drug eruption based on their cumulative experience of treating many patients, classified the rash phenotypes observed during the clinical course into the following categories: exfoliative dermatitis (ED), erythema multiforme (EM), and Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) (Ministry of Health of the People's Republic of China 2007) (Fig. 3.1). Though the rash was the same as that of severe cutaneous adverse reactions to drugs, 3/4 of the patients did not receive medication before the onset of the rash. The remaining 1/4 took medicines for cold because of the initial feverish symptoms (Huang et al. 2006). Of the rash phenotypes most prevalent one is ED. In severe cases, the rash develops into generalized edematous erythema, with facial swelling accompanied by exudates and incrustation, sometimes involving the oral mucous membrane. The rash darkens with increasing desquamation; the scales may be thick on the palm, and can be exfoliated like torn gloves (Ministry of Health of the People's Republic of China 2007).

Importantly, human herpesvirus 6 (HHV6) is reactivated in patients suffering from TCE HS. HHV6 is a causative of exanthema subitum during infancy, and remains latent within the body after the primary infection in most persons in all healthy populations (Yoshikawa et al. 1989; Asano et al. 1989; Yamanishi et al. 1988).

Table 3.1 Clinical characteristics of trichloroethylene hypersensitivity syndrome

Clinical features	Note
Incidence	Less than 1–13 % of the occupationally exposed population (Kamijima et al. 2007). What determines the incidence remains unclear. Both exposure dose (average and peak exposure concentration) and susceptible gene polymorphism (see below) may be involved
Interval from commencement of exposure to disease onset	Four weeks on average, mostly 2–6 weeks, and almost all within 3 months (Huang et al. 2002, 2006; Kamijima et al. 2007)
Initial symptoms	Fever and/or rash (Huang et al. 2002, 2006; Kamijima et al. 2007)
Fever	Frequent (>38 °C) (Huang et al. 2002, 2006; Kamijima et al. 2007)
Rash	Different phenotypes were reported: exfoliative dermatitis (ED) type, erythema multiforme (EM) type, Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) type. ED type is most frequently observed (Huang et al. 2002, 2006; Kamijima et al. 2007). ED and TEN are associated with higher-level human herpesvirus 6 (HHV6) reactivation and stronger proinflammatory cytokine responses (Kamijima et al. 2013)
Mucosal lesion	Possible (Huang et al. 2002, 2006; Kamijima et al. 2007)
Lymphadenopathy	Frequent (cervical nodes, axillary nodes, inguinal nodes and others) (Huang et al. 2002, 2006; Kamijima et al. 2007)
Eosinophilia ($>1.5\times10^9$/L)	Possible. In cases whose eosinophilia is not evident, leucocytosis ($>11\times10^9$/L) is frequently observed (Kamijima et al. 2007; Huang et al. 2006)
Hepatitis	Most patients suffer and it can be a cause of fatality. Jaundice is frequently observed (Huang et al. 2002, 2006; Kamijima et al. 2007)
Possible other organ involvement	Heart, lung, spleen, adrenal gland, larynx and brain (encephalitis) (Kamijima et al. 2007; Huang et al. 2006)
Reactivation of latent viruses/co-infection	HHV6 and cytomegalovirus following HHV6 reactivation (Huang et al. 2006; Watanabe et al. 2010; Watanabe 2011). Other betaherpesvirinae of which the reactivation has been reported in DIHS/DRESS patients can be reactivated (Watanabe et al. 2010; Watanabe 2011; Yanagiba 2007). Increase in IgM antibody titer against measles virus was also reported (Huang et al. 2006)
Percent fatal	9–13 % (Kamijima et al. 2007). Extensive use of corticosteroid can decrease the fatality(Kamijima et al. 2013)
Factor(s) determining individual susceptibility	*HLA-B*13:01* and *HLA-B*44* are the reported major determinant (Li et al. 2007). See Table 3.2 for more details
Positive skin patch test results	Trichloroethanol (0.005 %) (Watanabe et al. 2010; Nakayama et al. 1988), trichloroacetic acid (5 %) (Watanabe et al. 2010), chloral hydrate (5 %) (Watanabe et al. 2010)

Milder cases may lack the above typical features

The reactivation frequency in TCE HS patients has been reported to be at least about 90 % (Kamijima et al. 2013). This finding indicated that the pathophysiology of occupational TCE HS was exactly the same as that of DIHS or DRESS (Huang et al. 2006; Watanabe et al. 2010; Watanabe 2011; Kamijima et al. 2013). DIHS is characterized by (1) maculopapular rash developing >3 weeks after starting with a limited number of drugs, (2) prolonged clinical symptoms 2 weeks after discontinuation of

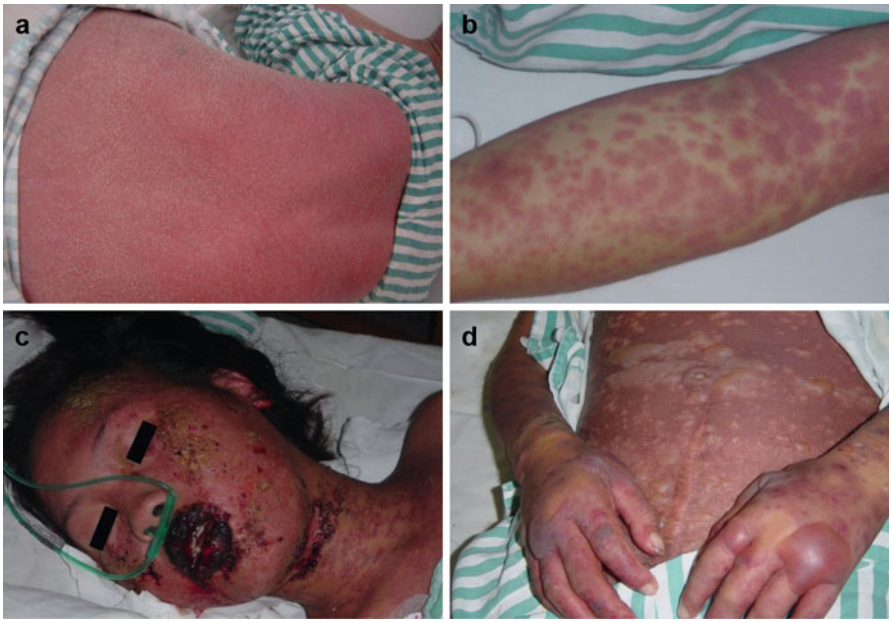

Fig. 3.1 Representative cutaneous manifestations of trichloroethylene-induced generalized hypersensitivity dermatitis. (**a**) Exfoliative dermatitis type, (**b**) Erythema multiforme type, (**c**) Stevens-Johnson syndrome type, (**d**) Toxic epidermal necrolysis type. Rash phenotypes were classified according to the 'Diagnostic criteria of occupational medicamentose-like dermatitis due to trichloroethylene' (GBZ 185–2006) developed by the Ministry of Health of the People's Republic of China (2007) (This figure originally appeared in a previous article (Huang et al. 2006) and was reproduced with permission)

the causative drug, (3) fever (>38˚C), (4) liver abnormalities, (5) leucocyte abnormalities being exhibited as either leucocytosis, atypical lymphocytosis or eosinophilia, (6) lymphademopathy, and (7) HHV6 reactivation. A patient is diagnosed as typical DIHS when these seven criteria are met and as atypical DIHS when five (1–5) criteria are met (Shiohara et al. 2007). Thus, most of the cases reported in the past meet the diagnostic criteria of DIHS (Watanabe 2011), although our previous study was the first to detect HHV6 reactivation (Huang et al. 2006). The notion has been fully established that TCE is a causative agent of DIHS (Huang et al. 2006; Watanabe 2011; Kamijima et al. 2013).

3.3.2 Human Herpesvirus 6 Reactivation and Inflammation-Related Cytokines

Interestingly, HHV6 viral load in the blood was associated with the rash phenotype; its viremia was more frequently observed and the maximum HHV6 DNA copy numbers were higher in patients with ED than in those with EM type. Patients with TEN type rash also showed a higher-level of reactivation (Kamijima et al. 2013).

The reactivation of HHV6 in the clinical course of DIHS/DRESS is one of the major concerns for achieving a better treatment outcomes since the prognosis of the disease depends on whether or not the reactivation can be controlled (Hashimoto et al. 2003; Shiohara et al. 2006). In patients with TCE HS, levels of blood cytokines, i.e., tumor necrosis factor (TNF) -α, interferon (IFN)-γ, interleukin (IL)-5, IL-6, and IL-10, are significantly and remarkably higher than in healthy TCE-exposed workers (Kamijima et al. 2013; Okamura et al. 2007; Ito et al. 2007). Jia et al. also reported that serum levels of TNF-α, IL-1β, IL-6 and IL-8 in TCE HS patients were significantly higher than in TCE-exposed workers and non-exposed controls (Jia et al. 2012). Their team found that a TCE metabolite trichloroethanol, but not trichloroacetic acid (TCA), increased the release of IL-1α and IL-6 in a keratinocyte cell line in a dose-dependent manner (Jia et al. 2012). In contrast, healthy workers occupationally exposed to TCE reportedly showed lower IL-4 and higher IFN-γ and IL-2 levels in their serum (Iavicoli et al. 2005). IL-10 concentrations in exposed workers were also lower than in unexposed controls whereas there were no significant differences for TNF-α and IL-6 (Bassig et al. 2013). In inflammatory responses of TCE HS, a contribution by the gene polymorphism of TNF-α (G-308A) to disease predisposition was reported (Dai et al. 2004). A TNF-α concentration upon hospitalization higher than 3 standard deviations above the mean value of healthy exposed workers was significantly associated with a subsequent or simultaneous increase in HHV6 DNA in the clinical course (odds ratio 22.4) (Kamijima et al. 2013). Elevation of TNF-α and IL-6 levels reportedly preceded HHV6 reactivation in DIHS (Yoshikawa et al. 2006). It was also shown that HHV6 upregulates the production of TNF-α in peripheral blood mononuclear cells (Flamand et al. 1991). Thus, it may be likely that TCE exposure affects the immunological condition of exposed workers, and that once the TCE HS has occurred in a susceptible worker, the increased TNF-α might induce HHV6 reactivation, or vice versa, resulting in the manifestation of a specific rash phenotype. In addition to the reactivation of HHV6, that of cytomegalovirus (Watanabe et al. 2010) and HHV7 (Yanagiba 2007) can be detected as well. However, co-infection/reactivation of viruses other than betaherpesvirinae is not usually observed. In patients with DIHS, flaring of symptoms such as fever and hepatitis was closely related to HHV6 reactivation during the clinical course after cessation of the causative medication (Tohyama et al. 2007). The same phenomenon is observed in the clinical courses of patients suffering from TCE HS, even after TCA has become undetectable in their urine.

3.3.3 Liver Dysfunction

Another important characteristic of TCE HS is liver dysfunction that is observed in most of the patients. Systematic investigation of possible risk factors for hepatitis, e.g., hepatitis A, B, and C viruses, alcohol consumption, drug abuse, use of sanitary chemicals, drinking unsanitary water, and past and family history of allergic, immunological or hepatocystic diseases, ruled out the involvement of these factors in the disease. C-reactive protein and the erythrocyte sedimentation rate usually show

negative results (Huang et al. 2006), as does the antinuclear antibody detection test (Kamijima et al. 2013), which is different from those of active autoimmune diseases such as systemic lupus erythematosus.

Some of the chlorinated hydrocarbons are known to have hepatotoxicity although their inherent toxicity varies depending on the chemicals. Exposure to high concentrations of TCE in the air could induce liver dysfunction (World Health Organization (WHO) 1985), but the effects on the liver are generally not massive in those who were anesthetized with TCE or who were occupationally exposed to TCE (Agency for Toxic Substances and Disease Registry 1997), which could have been due to activation of peroxisome proliferator-activated receptor α (Ramdhan et al. 2008; Ramdhan et al. 2010). In contrast, the hepatitis observed in TCE HS is induced by exposure at much lower concentrations and can be a life-threatening fulminant one; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels can increase to several thousand U/L. Unfortunately, biopsy results which could address the immune-mediated component of the hepatotoxicity have not been reported in the literature.

The two types of TCE-induced hepatitis mentioned above have different pathophysiologies. An experimental rodent study clearly showed that TCE can induce two different types of hepatitis in guinea pigs, i.e., acute-type toxic hepatitis and immune-mediated hepatitis (Tang et al. 2008). The former type was observed in a dose-dependent manner; in an experiment where guinea pigs received intradermal TCE injections of 0, 167, 500, 1,500 or 4,500 mg/kg, the increase in AST was significant at and above TCE dosages of 1,500 mg/kg, and the increase in ALT and evident fatty degeneration, hepatic sinusoid dilation and inflammatory cell infiltration were observed at 4,500 mg/kg (Tang et al. 2008). A mechanistic study using knockout mice lacking cytochlome P450 (CYP) 2E1 suggested that CYP 2E1-mediated bioactive TCE metabolite(s) might induce nuclear factor kappa B (NFκB) (p52), leading to hepatic inflammation due to the high TCE exposure (Ramdhan et al. 2008). Some intermediate metabolite of TCE to chloral hydrate is considered to play a major role in the hepatotoxicity (Nakajima et al. 1988). In contrast, histopathological findings of the animals sensitized with TCE in guinea pig maximization test (GPMT) were different from the above findings; they were characterized by diffuse ballooning changes without lymphocyte infiltration and necrotic hepatocytes. In addition, 90.9 % (30/33) of sensitized guinea pigs revealed either ALT or AST levels higher than the upper limits of reference values, while 88.2 % (15/17) of guinea pigs without sensitization showed both AST and ALT levels below the limits (Tang et al. 2008). Thus, it appears that low-dose exposure to TCE can induce hepatic damage only by means of immune-mediated mechanisms, which is under investigation in ongoing studies. This experimental evidence suggests that the mechanisms of hepatotoxicity due to TCE are not unique, and that the hepatitis observed in TCE HS, which can be life-threatening, should be treated from the viewpoint of an immune-mediated mechanism. Use of an extensive dose of corticosteroid is reportedly effective (Table 3.1). For example, a series of patients have been treated with methylprednisolone at an initial daily dosage of 80–250 mg with progressive tapering, depending on the clinical severity and response to the treatment (Kamijima et al. 2013).

3.4 Trichloroethylene as a Causative Agent of Hypersensitivity Syndrome

Although a considerable number of reported cases suggested a causal relationship between TCE exposure and the disease, the question of whether the causative agent was TCE itself or the impurities/stabilizers/contaminant(s) of the solvent was a controversial issue, because commercial solvent products used in workplaces are generally not 100 % pure. Impurities depend on the manufacturing route, the type and quality of feed stock used, the type of distillation equipment, and the level of compliance with technical specifications (World Health Organization (WHO) 1985). Stabilizers, some of which have skin sensitization potency (Wahlberg and Adams 1999), are added to prevent the solvent from breaking down into hydrochloric acid, which can corrode the parts being cleaned and the cleaning equipment itself (Mohr 2001). However, today there are the following lines of evidence establishing the causal relationship between TCE itself and TCE HS (Kamijima et al. 2008). First, TCE metabolites, especially TCA, were detected in all the patients' urine when urine was sampled within the period of several times its biological half-life of 57.6 h (Ikeda and Imamura 1973). Second, a comprehensive survey of the solvent constituents including impurities, stabilizers, and metals, as well as the airborne chemicals, showed that no chemical except for TCE was commonly detected in the patients' workplaces. Third, it was confirmed that TCE had a strong sensitization potential in GPMT. This model for type IV hypersensitivity (Kimber et al. 2002) revealed sensitization rates of 66–71 %, showing erythema and skin edema and immune-mediated liver injury at doses below those inducing acute toxic liver injury (Tang et al. 2002; Tang et al. 2008). Skin patch test conducted in a limited number of patients showed positive results at least for TCE metabolites at low concentrations (0.005 % trichloroethanol) (Table 3.1) (Watanabe et al. 2010; Nakayama et al. 1988).

One important viewpoint in the field of occupational health is that some patients themselves did not use TCE but worked close to degreasing tubs (Goon et al. 2001; Kamijima et al. 2013). In a case in China, a patient after recovery suffered from rash again only from a short-time visit to the person's workplace to pick up the belongings. This indicates that skin contact with liquid TCE is not essential for the onset of this skin disorder, which is completely different from solvent-induced irritant dermatitis due to its defatting action (Kamijima et al. 2007). This notion is supported by the fact that oral administration of chloral hydrate, a metabolite of TCE used as a sedative, could also induce generalized skin eruption equivalent to TCE HS (Lindner et al. 1990).

3.5 Susceptible Population

An important feature of TCE HS is the remarkable difference in individual susceptibility to the disease. When an exposed worker does not suffer from it within 3 months after commencement of an extensive exposure to TCE, it can be said that he/she is tolerant to TCE HS. Thus, there should be genetic risk factors leading to

Table 3.2 Genetic factors reported as candidate biomarkers of individual susceptibility

Gene polymorphisms	OR (95 % Cl)	Note	References
*HLA-B*13:01*	27.5 (13.5–55.7)	*B*13:01 or B*44* : OR 36.8 (95%CI 17.8–76.1)	Li et al. (2007)
*HLA-B*44*	20.1 (2.6–157.5)		
NAT1 (SS)	1.10 (0.52–2.34)	*NAT1* (SS) and *NAT2* (FS + SS): OR 2.71 (95%CI 1.29–5.70)	Dai et al. (2009)
NAT2 (FS + SS)	2.01 (1.14–3.54)		
*ALDH2 * 1/ * 2* and *ALDH2 * 2/ * 2*	0.5 (0.29–0.85)		Li et al. (2006)
TNF A I/II (TNF-α *-308* site)	0.398 (0.164–0.967)	*TNF A I*: wild-type allele	Dai et al. (2004)

Abbreviations. ALDH aldehyde dehydrogenase, *95 % CI* 95 % confidence interval, *FS + SS* intermediate or slow acetylators, *HLA* human leucocyte antigen, *NAT* N-Acetyltransferases, *OR* odds ratio

ways to search for a biomarker of individual susceptibility, focusing on gene polymorphisms (Dai et al. 2004; Nakajima et al. 2003; Li et al. 2007). One approach was to focus on polymorphisms of drug-metabolizing enzymes (Nakajima et al. 2003). The polymorphisms investigated so far were CYP1A1, CYP2E1, glutathione S-transferase (GST), alcohol dehydrogenase (ADH), aldehyde dehydrogenase (ALDH), and two genes (*NAT1* and *NAT2*) that encode *N*-acetyltransferases (NATs) (Table 3.2). Another focus was human leukocyte antigen (HLA). Associations of HLA-DM and HLA-B with TCE HS have been reported, and the investigation of the latter revealed remarkable success. Li et al. reported HLA-B*13:01 and HLA-B*44 as biomarkers of individual susceptibility with an odds ratio of 36.8 in a patient group having either of the HLA loci (Table 3.2) (Li et al. 2007). This is a finding analogous to carbamazepine-induced SJS/TEN and allopurinol-induced severe cutaneous adverse reactions in which strong associations with HLA-B*15:02 (Chung et al. 2004) and HLA-B*58:01 (Hung et al. 2005), respectively, were reported. Today, candidate peptides bound to the HLA-B*13:01 molecule have been identified (Zhang et al. 2013).

3.6 Preventive Measures of Trichloroethylene Hypersensitivity Syndrome from the Viewpoint of Dose–Response Relationship

Generally speaking, ambient air monitoring is a good measure for assessing external exposure to a solvent. In 2007, the Time-Weighted-Average (TWA) Threshold Limit Value (TLV) of TCE, set by the American Conference of Governmental Industrial Hygienists (ACGIH), was reduced from 50 ppm (270 mg/m^3) to 10 ppm (54 mg/m^3) to protect against effects on the central nervous system (CNS), as well as other potential effects including renal toxicity and cancer. A TLV-short-term exposure limit (STEL) of 25 ppm (135 mg/m^3) was also recommended because the CNS effects of TCE appeared to be related to peak exposures (American Conference of Governmental Industrial Hygienists 2007). However, prevention of TCE HS is

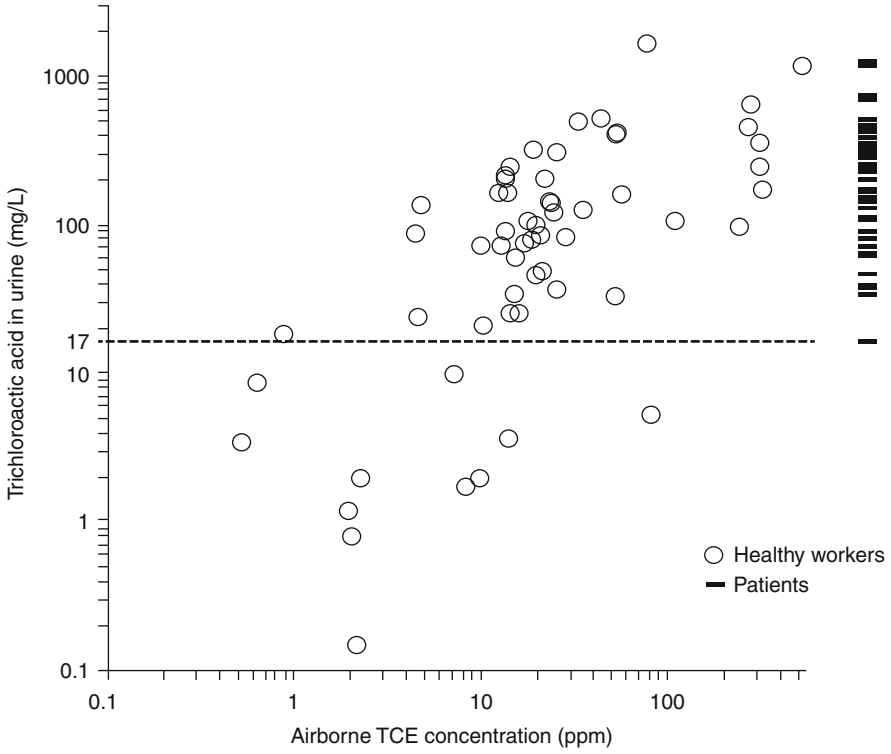

Fig. 3.2 End-of-shift trichloroacetic acid (TCA) concentrations (mg/L, *vertical axis*) in urine of patients (n = 42, *bars*) and healthy workers (n = 59, *circles*) occupationally (directly or indirectly) exposed to TCE. For healthy workers, 8-h time-weighted average personal exposure concentrations (ppm, *horizontal axis*) were also shown, but concentrations were not available for patients. End-of-shift TCA concentrations of the patients were estimated from the concentrations on the day of hospitalization (Kamijima et al. 2008; Kamijima et al. 2013)

not considered in the current documentation. Thus, this section aims to primarily address TCE exposure dose that could elicit hypersensitivity skin reactions.

In the previous case reports, airborne personal exposure concentrations of each patient were usually not available. The only way to directly assess a patient's personal exposure was to measure TCE metabolites in urine. However, measurements were not conducted in most of the case reports published in the last century probably because the importance of biological monitoring at the initial clinical stage of the disease was overlooked. Another problem was that urine available from patients were usually not end-of-shift, so as to enable a comparison of the metabolite concentration with its biological exposure index (BEI). Then we investigated airborne personal exposure concentrations of TCE and TCA concentrations in end-of-shift urine of the healthy workers who worked in the same workplaces as the patients (Fig. 3.2) (Kamijima et al. 2008). On the other hand, we estimated the end-of-shift concentration of hospitalized patients' urine based on information of the time period between the end of shift and the urine collection, on the assumption that the

biological half-life of urinary TCA did not vary between patients. The estimated average urinary TCA concentration at the end of their shift was 206 mg/L (95 % confidence interval 78–542 mg/L) (Kamijima et al. 2008). Another estimation from a different patient group showed similar results: 238 mg/L (arithmetic mean) or 153 mg/L (geometric mean) (Kamijima et al. 2013). Thus, it was revealed that many of the patients suffering from TCE HS were extensively exposed to TCE. However, Fig. 3.2 clearly shows that the concentration ranges of the patients and healthy workers widely overlap. The mechanism by which susceptible individuals suffer from the disease should be clarified further.

The next discussion is about the threshold TCA concentration of the patients, which provides useful information for preventing TCE HS. As shown in Fig. 3.2, the lowest end-of-shift concentrations estimated using the reported biological half-life of 57.6 h (Ikeda and Imamura 1973) was 17 mg/L (Kamijima et al. 2013). It is recommended that urinary TCA concentrations be kept below the ACGIH BEI value of 15 mg/L to better prevent TCE HS in susceptible workers.

3.7 Future Directions: Issues Remaining to Be Solved

As discussed above, substantial knowledge about TCE HS has accumulated during this century. The following are examples of the remaining questions. The first concerns the threshold exposure dose that could elicit the disease. More comprehensive studies may be necessary to answer the question of whether the current BEI value is effective to protecting susceptible individuals, especially according to the HLA-B*13:01 status. The second question is whether or not TCE exposure is the only trigger of the sensitization process in susceptible individuals. This question remains to be answered since clusters of disorder occurrence in a workshop during a short period, even within a half month in some cases, have been reported from several countries so far (Hisanaga et al. 2002; Lin et al. 2003; Kamijima et al. 2007). Unrevealed work-related factor(s) other than TCE exposure and genetic factors might have played a supplementary role in causing or developing the disease.

3.8 Conclusions

Occupational diseases are theoretically preventable. It is a great pity that dozens of predisposed workers lost their lives due to TCE HS. The fatalities resulted from lack of knowledge that this disease is immune-mediated. The sensitized victims continued working in the same workplace even after onset of the disease, i.e., they continued being exposed to TCE, or returned to the same work after they recovered from the illness. Such a tragedy should not be repeated in any part of the world.

At present, if replacement of TCE by a safer substitute is not a realistic measure, the best preventive strategy for this disease is to control the exposure under the understanding that TCE is an allergen. A sensitizer notation is necessary for the

occupational hygiene standards of TCE. Available evidence suggests that biological monitoring of urinary TCA, which is superior to trichloroethanol because the biological half-life of TCA is longer, is preferable to environmental measurement. It is recommended that the exposure be controlled so as to keep the urinary TCA concentration below the ACGIH BEI value of 15 mg/L in the end-of-shift urine in order to reduce the risk of TCE HS. Education to enforce better occupational hygiene practices is also necessary to reduce the exposure.

For early detection of the disease, occupational health professionals should pay careful attention to initial symptoms of the disease, especially fever, rash and jaundice. Exposed workers should be informed of the initial symptoms of the disease as well. Clinicians are requested to ask about solvent exposure history from patients who suffer from generalized rash like drug hypersensitivities.

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