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REVIEW

Occupational trichloroethylene exposure as a cause of idiosyncratic generalized skin disorders and accompanying hepatitis similar to drug hypersensitivities

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Abstract
Objectives Workers exposed to trichloroethylene (TCE) rarely show severe generalized skin disorders and accompanying hepatitis which resemble drug hypersensitivities. The disorders are completely different from solvent-induced irritating contact dermatitis, and their serious consequences have become one of the critical occupational health issues recently in Asia. The present review sheds light on the analogous relationship between the reported patients' clinical manifestations and those of severe drug rash, and provides a comprehensive picture of the disorder occurrences among TCE-exposed workers to date.
Methods All literature published in English and ad hoc publications in local languages were reviewed.
Results The patients typically showed rash on the extremities, face, neck or trunk with/without fever 2 weeks to 2 months after commencement of occupational TCE exposure. Reported cutaneous manifestations were classified into two hypersensitivity categories, i.e. hypersensitivity syndrome and erythema multiforme/Stevens–Johnson syndrome/toxic epidermal necrolysis. Based on this categorization, 124 (52%) cases were classified as the former and 115 (48%) as the latter. According to the two spectra, the prevalence of each clinical finding of TCE-related skin disorders was close to that in drug hypersensitivities except for disease incidence and the prevalence of fever, hepatitis, and lymphadenopathy. Occurrences of the disorders have been reported from the USA, Japan, Spain, Singapore, China, Korea, Thailand, and the Philippines. The case reports from industrialized countries were mostly published up to 1990, whereas cases from Asian industrializing countries appeared thereafter.
Conclusions The TCE-related generalized skin disorders are important not only in terms of the number of disease occurrences and severity but from the viewpoint of drug hypersensitivity. Systematic collection of clinical information is necessary in cases diagnosed by the same criteria as those used for drug hypersensitivities. Detailed exposure assessments are also required to establish preventive strategies in these countries.

Keywords Trichloroethylene · Occupational exposure · Hypersensitivity syndrome · Stevens–Johnson syndrome · Hepatitis

Abbreviations

TCE	Trichloroethylene
ED	Exfoliative dermatitis
HS	Hypersensitivity syndrome
EM	Erythema multiforme
SJS	Stevens–Johnson syndrome
TEN	Toxic epidermal necrolysis
TCA	Trichloroacetic acid

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Introduction

Organic solvents are responsible for as much as 20% of occupational dermatitis cases. Most of the adverse skin effects of solvents are attributable to irritation based on their local defatting action, i.e. dissolution of the skin surface lipids, the lipid material in the stratum corneum, and the fatty fraction of the cell membranes. Allergic contact dermatitis is rare (Wahlberg and Adams 1999). In contrast, workers exposed to trichloroethylene (TCE) rarely show far more severe skin manifestations than irritating contact dermatitis, i.e. generalized skin disorders often accompanying grave hepatitis, which resemble drug hypersensitivities. These TCE-related hypersensitivities are totally different from typical solvent toxic effects in terms of unclear dose–response relationship, period of exposure before disease onset, generalized rash, fever, lymphadenopathy, and recurrence just after minimal re-exposure (Hisanaga et al. 2002; Huang et al. 2002; Nakajima et al. 2003).

The number of cases reported with these occupational skin disorders has been increasing after the mid-1990s in Asia, especially in China, as shown in Table 1 listing the publication years of case reports. Though TCE still plays a significant role as a degreasing solvent even in developed countries (Ukai et al. 1997), and serious consequences of the disorder have become one of the critical occupational health issues recently in Asia, the disorders have thus far drawn little attention worldwide. Moreover, whether or not TCE itself can be a direct cause of generalized allergic disorders remains open to question regardless of the considerable number of reported cases suggesting a link between the exposure and the disease.

We previously published two reviews aiming to clarify the relationship between TCE exposure and these disorders. The initial review, written in Japanese with an abstract and tables in English, first clarified that increasing case occurrence of TCE-related generalized skin disorders in Asia since mid-1990s had become an important occupational health issue in the region (Hisanaga et al. 2002). The second review discussed the possible skin disorder mechanisms from the viewpoint of drug-metabolizing enzymes and their genetic polymorphisms (Nakajima et al. 2003). The focus of the present article is twofold: to shed light on the analogous relationship between the reported patients' clinical manifestations and those of severe drug rash of which the pathogenesis has been understood fairly well, and to provide a comprehensive picture of the TCE-related generalized skin disorder occurrences especially in Asian countries up to the present. Contact dermatitis and hepatitis not accompanied by generalized dermatitis are outside the scope of this review paper.

Clinical manifestations and classification of TCE-related generalized skin disorders

Patients suffering from TCE-related generalized skin disorders typically show rash on the extremities, face, neck or trunk with/without fever 2 weeks to 2 months after commencement of occupational TCE exposure (Bauer and Rabens 1974; Bond 1996; Chae et al. 2003; Chittasobhaktra et al. 1997; Goon et al. 2001; Hisanaga et al. 2002; Hu et al. 2003; Huang et al. 2002; Kang et al. 1999; Kubota 1966; Li et al. 1998; Nakayama et al. 1988; Pantucharoensri et al. 2004; Phoon et al. 1984; Shi and Ma 2005; Xia et al. 2004; Wang and Yu 2005). Chinese researchers in the field of occupational and clinical medicine established a diagnostic standard (GBZ18-2002 4.1.5 defined by the Ministry of Health, People's Republic of China) for these TCE-related skin disorders based on their cumulative experience in treating patients. They noted analogous relationships between the patients' skin manifestations and those of generalized drug eruption, and found that the former could be classified into the following four categories as the latter comprising several phenotypes: (1) exfoliative dermatitis (ED), (2) erythema multiforme (EM), (3) Stevens–Johnson syndrome (SJS), and (4) epidermolysis bullosa (Dai et al. 2004; Huang et al. 2002) or toxic epidermal necrolysis (TEN) (Xia et al. 2004). Keeping the above classification in mind, we grouped each reported cutaneous manifestation into two broad spectra, hypersensitivity syndrome (HS) or EM/SJS/TEN (Table 2), based on the notion that the different clinical patterns of severe drug eruptions probably suggested different mechanisms of cutaneous reaction (Roujeau 2005).

Drug-induced HS, a delayed type of allergic reaction, is distinguishable from other types of drug hypersensitivities including SJS/TEN, and typically characterized by the following features: (1) development within 2 months of the initiating therapy; (2) fever and a skin rash are frequently the first signs; (3) cutaneous manifestations usually begin as a morbilliform eruption; (4) the face, upper trunk, and upper extremities are the first body parts to be affected and the lower extremities later become involved; (5) erythroderma may occur, and the maculopapular eruption later becomes infiltrated and indurated with an edematous follicular accentuation; (6) there is no necrosis in the epidermis, which is different from TEN; (7) sterile

Table 1 Year of publication and number of cases reported in each country

Region	Country	Total number of reported cases	<1969	1970–1979	1980–1989	1990–1999	>2000
Asia	China (including Taiwan)	More than 200				Joson et al. (1998) ($N = 57$); Li et al. (1994) ($N = 5$); Li et al. (1998) ($N = 45$)[c]	Hu et al. (2003) ($N = 2$); Dai et al. (2004) ($N = 111$)[d]; Wang et al. (2004) ($N = 3$); Xia et al. (2004) ($N = 61$)[c,d]; Shi and Ma (2005) ($N = 5$); Wang and Yu (2005) ($N = 1$)
	Korea	2				Kang et al. (1999) ($N = 2$)[e]	Chae et al. (2003) ($N = 1$)[e]
	Japan	5	Kubota (1966) ($N = 2$); Tateishi et al. (1969) ($N = 1$); Tanaka et al. (1969) ($N = 1$)[a,b]	Midorikawa et al. (1972) ($N = 1$)[a,b]	Nakayama et al. (1988) ($N = 1$)		
	Phillipines	7				Estrella-Gust et al. (1999) ($N = 7$)	
	Singapore	8			Goh and Ng (1988) ($N = 1$) Phoon et al. (1984) ($N = 5$)	Tan et al. (1997) ($N = 1$)	Goon et al. (2001) ($N = 1$)
	Thailand	3				Chittasobhaktra et al. (1997) ($N = 1$)	Pantucharoensri et al. (2004) ($N = 2$)
Europe	Spain	1			Conde-Salazar et al. (1983) ($N = 1$)		
North America	USA	5		Bauer and Rabens (1974) ($N = 4$)		Bond (1996) ($N = 1$)	

[a] The case information appeared in a grant report and a conference abstract written in Japanese (Hisanaga et al. 2002)

[b,c,d,e] The same cases were reported by different authors

Table 2 Classification of reported cases of trichloroethylene-related generalized skin disorders

	Hypersensitivity syndrome (HS)	EM/SJS/TEN	Unclassified
Number of cases[a]	124 (male 11, female 2, unknown sex 111)	115 (male 7, female 63, unknown sex 45)	21 (male 10, female 11)
References	Kubota (1966) ($N = 2$), Bauer and Rabens (1974) ($N = 4$), Conde-Salazar et al. (1983) ($N = 1$), Nakayama et al. (1988) ($N = 1$), Goh and Ng (1988) ($N = 1$), Bond (1996) ($N = 1$), Chittasobhaktra et al. (1997) ($N = 1$), Li et al. (1998) ($N = 36$), Goon et al. (2001) ($N = 1$), Dai et al. (2004) ($N = 75$), Wang and Yu (2005) ($N = 1$)	Midorikawa et al. (1972)[b, c] and Tanaka et al. (1969)[c] (SJS, $N = 1$), Phoon et al. (1984) (SJS, $N = 4$), Tan et al. (1997) (TEN, $N = 1$), Li et al. (1998) (EM, $N = 3$; SJS/TEN $N = 6$), Joson et al. (1998) (SJS, $N = 57$), Estrella-Gust et al. (1999) (SJS, $N = 7$), Dai et al. (2004) (EM, $N = 33$; SJS/TEN, $N = 3$)	Tateishi et al. (1969) ($N = 1$), Phoon et al. (1984) (HS/SJS, $N = 1$), Li et al. (1994) ($N = 5$), Kang et al. (1999) ($N = 1$), Kang et al. (1999)[d] and Chae et al. (2003)[d] ($N = 1$), Hu et al. (2003) ($N = 2$), Pantucharoensri et al. (2004) (SJS, $N = 2$), Wang et al. (2004) ($N = 3$), Shi and Ma (2005) ($N = 5$)

EM erythema multiforme, *SJS* Stevens–Johnson syndrome, *TEN* toxic epidermal necrolysis

[a] Cases in Guangdong, China, reported by Xia et al. (2004) were not counted since those suffering between 1997 and 2000 were included in Li et al. (1998) and Dai et al. (2004). Though the number of both sexes was not demonstrated in these reports, the authors described that there was no remarkable difference in the number of patients between the sexes. Note that Taiwanese cases (Joson et al. 1998) were all females since there was no male worker in the factories

[b] The case information was published as a grant report written in Japanese (Hisanaga et al. 2002)

[c,d] The same case was reported by different authors

follicle-centered pustules may exist as well as nonfollicular small pustules; (8) the eruption can become purpuric, mainly on the legs, and with resolution, desquamation occurs; (9) another clinical presentation is represented by ED which may be associated with mucosal involvement; (10) lymphadenopathy is frequent, and hepatitis is the most common visceral manifestation; and (11) hematologic abnormalities with hyperleucocytosis, eosinophilia, and mononucleosis-like atypical lymphocytes are common (Bocquet et al. 1996).

Thus, in the present review of TCE-related generalized skin disorders, cases were classified as HS when the descriptions of their skin manifestations were consistent with the above features (especially 1–5 and 9), or as the second spectrum, EM/SJS/TEN, when the authors of the original paper specified the above diagnoses. Otherwise, cases were not classified. In this classification, the three phenotypes (EM/SJS/TEN) were grouped together since the diagnosis made was based on the different diagnostic criteria used by different authors. Most medical textbooks in the last century considered that EM majus, SJS, and TEN belonged to the same spectrum of disorders, while today SJS and TEN are considered to be the same disease but with varying degrees of severity. However, EM majus is considered to differ from SJS/TEN (Letko et al. 2005) not only in severity but also in the patterns of lesions and causes (Auquier-Dunant et al. 2002). Based on this categorization, 124 (52%) cases of the classifiable 239 were considered HS (Table 2). If cases without specific descriptions of each clinical manifestation are excluded, 13 (72%) out of 18 may be classified as HS, which is consistent with the finding that ED was the most prevalent (80%) phenotype in Chinese cases (Huang et al. 2002).

Table 3 summarizes findings of TCE-related and drug-induced generalized skin disorders according to each skin phenotype. Prevalence of each clinical finding in TCE-related skin disorders was calculated as the number of applicable patients divided by the total number of those reported. The characteristics of TCE-related skin disorders were generally close to those in drug hypersensitivities, except for some differences in the prevalence of clinical findings. First, the disease incidence seems much higher in TCE-related skin disorders where the prevalence varies from 0.25 to 12.5% (Fig. 1). In this regard, it should be noted that prevalence was mostly calculated by dividing the number of cases by

Table 3 Findings of trichloroethylene-related and drug-induced generalized skin disorders

	Hypersensitivity syndrome (HS)		EM/SJS/TEN	
	Trichloroethylene	Drugs[a,b] (carbamazepine, allopurinol, antibacterial sulfonamides, and others)	Trichloroethylene	Drugs[a,b] (carbamazepine, allopurinol, antibacterial sulfonamides, and others)
Rash	Severe exanthematous rash (may become purpuric), exfoliative dermatitis, no necrosis in the epidermis, facial edema, erythroderma, pustules		Small blisters on dusky purpuric macules or atypical targets, epidermic necrosis, outer layer of total detatchment of ≤10% of body-surface area for SJS, and >30% for TEN	
Mucosal lesion	38%	Infrequent	Erosions usually at ≥2 sites	
Incidence	Less than 1–13% of the exposed workers	1 reaction/5,000 patients for antiepileptic agents	Less than 1–13% of the exposed workers	14 reactions/10,000 patients for carbamazepine
Typical interval from beginning of exposure/ medication to onset of reaction	Usually within 3 months, mostly 2–5 weeks	2–6 weeks	All within 3 months, mostly 2–5 weeks	1–3 weeks
Fever	73%	30–50%	8%	10–30% (SJS), nearly all (TEN)
Lymphadenopathy	38%	About 75% with antiepileptic drugs	8%	No
Eosinophilia ($>10^3$ per mm^3)	23%	30%	8%	No
Hepatitis	46[c]–94%[d]	51%	92[c]–94%[d]	Frequent
Possible other organ involvement	Heart, lung, spleen, adrenal gland, larynx, brain	Kidney (11%), heart, lung, thyroid, brain	Kidney, thyroid, repiratory tract, gastrointestinal tract, blood vessels	Kidney, repiratory tract, gastrointestinal tract
Percent fatal	9%	10%	13%	<5% (SJS), 30% (TEN)
Factor(s) determining individual susceptibility	Unknown	Unknown	Unknown	HLA-B*1502 (carbamazepine)[e], HLA-B*5801 (allopurinol)[f] for Han Chinese
Infection identified in association with rash	Unknown	Human herpesvirus 6[g], cytomegalovirus[h], Epstein–Barr virus[i]	Unknown	Herpes simplex virus[j,k], Mycoplasma pneumoniae[j]

EM erythema multiforme, *SJS* Stevens–Johnson syndrome, *TEN* toxic epidermal necrolysis

[a] Roujeau and Stern (1994)

[b] Bocquet et al. (1996)

[c] Calculated value (see text)

[d] Xia et al. (2004)

[e] Chung et al. (2004)

[f] Hung et al. (2005)

[g] Hashimoto et al. (2003)

[h] Aihara et al (2001)

[i] Descamps et al (2003)

[j] Leaute-Labreze et al. (2000)

[k] Auquier-Dunant et al. (2002)

that of workers engaged in the same work in the same factory at the time of disease onset. Since workers often change jobs frequently in Asian developing countries, the actual incidence was more likely to be closer to the values estimated by Conde-Salazar et al. (1983) and Huang et al. (2002), i.e. less than 1%, which is still at

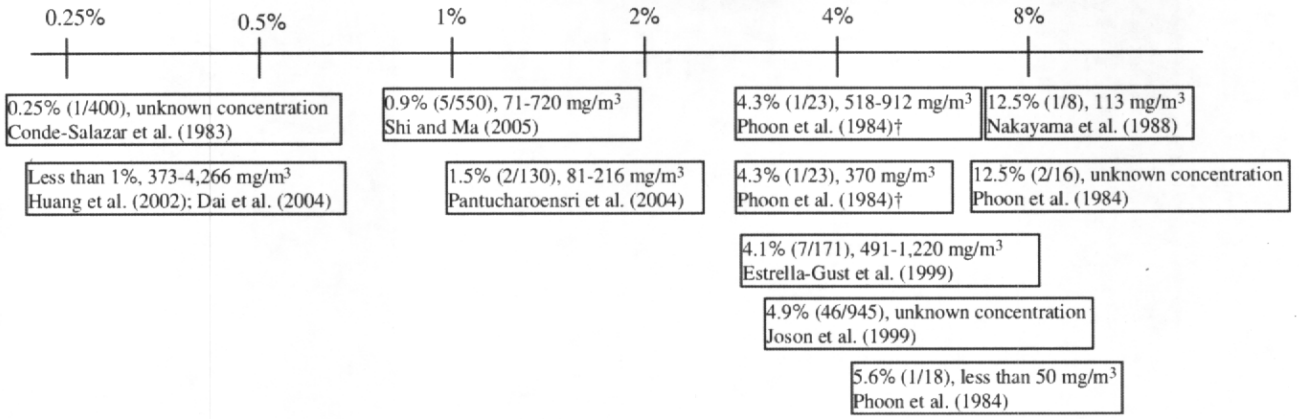

Fig. 1 Prevalence (numbers of patients/all the workers engaged in the same work in the same factory at the time of disease onset) of trichloroethylene-related generalized skin disorders and airborne trichloroethylene concentration in the workroom. In workplaces where more than one worker suffered from the disorders, intervals between disease onsets were within a year, mostly half a month. †Patients in the same room

least ten times higher than that of drug hypersensitivities. Second, the prevalence of hepatitis and fever also appeared to be higher in TCE-related HS than in drug-induced HS while that of lymphadenopathy appeared lower. However, it should be noted that the individual case reports did not necessarily mention whether or not the findings listed in the table were observed. With regard to hepatitis, Xia et al. (2004) reported that 94% of patients of the TCE-related generalized skin disorders in China had suffered from hepatitis.

Mortality was 9% in TCE-related HS and 13% in TCE-related EM/SJS/TEN patients, which was close to the corresponding figures observed in drug-induced generalized skin disorders (Table 3). Liver failure, infections, and the resulting sepsis were the principal causes of mortality (Hu et al. 2003; Kang et al. 1999; Pantucharoensri et al. 2004; Phoon et al. 1984) as well as in drug-induced generalized skin disorders (Letko et al. 2005). However, a few patients with TCE-related skin disorders reportedly died after hepatitis had improved, from exacerbation of the skin lesion (Goon et al. 2001) or from gastrointestinal bleeding and the resulting disseminated intravascular coagulation (Wang et al. 2004). The hepatitis observed in TCE-related generalized skin disorders was nonviral and apparently different in its clinical course from usual TCE-induced hepatitis, which occurs without showing rash at high concentrations (WHO 1985) in direct relation to P450-derived metabolites (Nakajima et al. 1988; Okino et al. 1991).

In drug hypersensitivities, etiological attribution of infectious diseases has been discussed (Table 3). The involvement of Herpes simplex virus and Mycoplasma pneumoniae in EM majus, SJS, and TEN has been reported (Auquier-Dunant et al. 2002; Leaute-Labreze et al. 2000). In addition, the similarity between viral skin eruption and the rash of drug-induced HS has led many researchers to seek an association between viral infection and drug hypersensitivity, though they are different diseases (Hashimoto et al. 2003). It has been postulated that infection by human herpesviruses may play a role in the development of drug-induced HS; human herpesvirus 6 (Hashimoto et al. 2003), cytomegalovirus (Aihara et al. 2001), and Epstein–Barr virus (Descamps et al. 2003) (Table 3). As for TCE-related skin disorders, hardly any of the human herpesvirus infections was examined with the exception of a few reports showing negative cytomegalovirus (Bond 1996) or EB virus titers (Wang and Yu 2005). Since the association between such infections and clinical courses including patient complications has been pointed out in drug-induced HS, the relation between above viral infection and the TCE-related skin disorders needs to be further examined in future studies.

Geographical distribution of cases suffering from TCE-related generalized skin disorders in past decades

Occurrences of the TCE-related disorders have been reported from the USA, Japan, Spain, Singapore, China, Korea, Thailand, and the Philippines, i.e. largely from Asia (Table 1).

Until 1970s: USA, Japan, and Singapore

The first description of TCE-related skin disorders was given by Schwartz et al. (1947) in an American textbook on occupational skin disorders 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". Though they did not mention possibly accompanying hepatitis and mucosal lesions, the above clinical features are reminiscent of those later associated with drug-induced HS. In 1974, Bauer and Rabens reported four cases of generalized cutaneous disorders in TCE-exposed workers in factories in the United States, all of whom were engaged in the cleaning of metals or bomb casings with TCE in a poorly ventilated plant. Their cutaneous manifestations were generalized papulovesicular eruption becoming an ED, or dry and scaling erythematous dermatitis originally involving hands and forearms and later becoming generalized scarlatiniform eruption with edema of face and eyelids (Bauer and Rabens 1974). All of the reported clinical features are in accordance with those of HS.

In Japan, the first cases of TCE-related generalized skin disorders were reported in 1966. Two workers engaged in cleaning tanks made of mild steel with TCE suffered rash with/without fever after their first 2–4 weeks on the job. They started work in the same factory in December 1965, and the exposure concentration was 54–270 mg/m^3 (10–50 ppm) with sporadic higher concentrations of 540–1,350 mg/m^3 (100–250 ppm). Urinary concentration of trichloroacetic acid (TCA) in one patient was 20.0 mg/l 30 days after the last exposure, and that in the other showed 40.0 mg/l 11 days after the last exposure. Both patients took a cold medicine containing pyrine, and later showed brawny erythroderma and desquamation. One patient showed recrudescence during his hospitalization (Kubota 1966). Their clinical manifestations corresponded to those of HS. The third case in Japan was a 38-year-old female worker. After exposure to TCE for 34 days in 1967, she developed facial edema, dyshidrosis-like rash, generalized erythema, fever, itch and rubor in the anus, external genitalia and oral cavity, cough, sputum, aphagia, and hepatomegaly. C-reactive protein was positive and the erythrocyte sedimentation rate was increased. Pathological findings after necropsy showed fatty degeneration and fibrosis of liver, chronic thyroiditis, membranous glomerulonephritis, ulcerative lesions in the oral cavity and rectum, and systemic thickening of the vascular tunica intima. The diagnosis made by the authors of this case report was SJS (Hisanaga et al. 2002). The fourth case reported at a regional conference in 1968 was an 18-year-old male who worked for an auto parts company. He cleaned machines with TCE [exposure concentration of 1,080 mg/m^3 (200 ppm)] and developed liver dysfunction, high fever, and a generalized pemphigoid rash, i.e. dark-colored erythema accompanying blisters. He also showed eosinophilia, mild lymphadenopathy, and congestion of conjunctiva, mouth, and pharynx (Tateishi et al. 1969).

In Singapore, the first cases were twin sisters aged 17 who started to work in a transistor factory in 1972. Among 16 workers in the same section, only the twins suffered from EM-like lesions with oral involvement along with abnormal hepatic function after working initially for about 3 weeks. The third case was a 24-year-old man suffering from EM-like lesions with oral involvement and abnormal liver function after working in a capacitor-manufacturing factory for about 5 weeks in 1979. His work was to service, adjust, reset and maintain the soldering machines, and occasionally to immerse ceramic components in a bowl of TCE. Of 23 workers in the same room, only he developed the disease. A skin biopsy revealed spongiosis with a damaged basement membrane, a perivascular mononuclear infiltrate, and marked upper dermal edema. The personal exposure concentration was 518–912 mg/m^3 (96–169 ppm). A patch test performed later with 5% TCE in olive oil showed negative (Phoon et al. 1984).

1980s: Singapore, Spain, Japan, and China

In the above Phoon et al. report from Singapore, the authors describe two more TCE-related generalized skin disorder cases during the 1980s (Phoon et al. 1984). The fourth case was a male aged 39, who developed a generalized maculopapular rash along with oral involvement and jaundice after about 3 weeks working in an electronic metal component factory in 1980. After hospitalization and discharge, he later returned to the job, but showed erythroderma developing into ED, eventually resulting in death from liver failure with septicemia. The airborne TCE concentration was later found to be less than 50 mg/m^3 (9 ppm), and urinary TCA concentrations of 18 production workers in the same factory ranged from 21 to 165 mg/l. The fifth case was a 17-year-old female machine operator in the same factory where the third case had worked. In 1981, she was the only one of 23 workers to develop a generalized EM-like rash accompanied by oral ulceration and jaundice after her first 2 weeks on the job, about 2 years after the third case had died. The rash later exfoliated with an exposure concentration around 370 mg/m^3 (69 ppm) before the disease onset, and 108–205 mg/m^3 (20–38 ppm) thereafter. Personal exposure concentrations of her fellow workers ranged 10–70 mg/m^3 (2–13 ppm). In 1988, Goh and Ng reported a much

milder case also from Singapore, a 29-year-old male, who had been engaged in cleaning barrels containing TCE for about 1 year. He presented with recurrent erythematous and xerotic plaques of the arms and trunk following inhalation of TCE vapor. A skin biopsy showed nonspecific dermatitis, a superficial perivascular lymphohistiocytic infiltrate in the upper dermis and parakeratosis in the epidermis. The authors diagnosed it as a mild form of ED (Goh and Ng 1988).

In Spain, a 25-year-old female case was reported in 1983. The patient worked for 8 years together with 400 employees of a cutlery factory in contact with various cleaning and storage products including TCE. She occasionally experienced intense itching all over her body at work, and erythematous pustular lesions appeared later to develop into ED. A challenge test of TCE exposure revealed recurrence of the clinical features without detectable levels of blood and urinary TCE metabolites, and a skin biopsy of vesiculopustular lesion showed subcorneal spongiform pustules with a light perivascular infiltration in the upper dermis. A patch test with 5% TCE in olive oil induced a red, scaly reaction. An increase of IgE (920 U/ml) was observed (Conde-Salazar et al. 1983).

In Japan, Nakayama et al. (1988) reported on a 21-year-old male case suffering from a high fever followed by generalized maculopapular rash on the 18th day after commencement of TCE exposure in a printing shop. He also showed liver dysfunction and eosinophilia, and his skin lesions developed into erythroderma and ED (Nakayama et al. 1988). These clinical manifestations are in accordance with typical HS. Closed patch test conducted 4 months after discharge revealed positive results for 10 and 25% TCE in olive oil and 0.005, 0.05, and 5% trichloroethanol in water, and negative results for 5% TCA in water, whereas ten control subjects manifested negative results to 5 and 25% TCE, 5% trichloroethanol, and 5% TCA. Seven other employees in the same workplace did not develop the patient's symptoms (Nakayama et al. 1988). The patient's work was to wipe off ink stains under the TCE exposure concentration of 113 mg/m^3 (21 ppm). He was also exposed to isopropyl alcohol at the concentration of 51 mg/m^3 (20 ppm) (Hisanaga et al. 2002).

Guangdong Province, China, is the region where 10% of the occupational intoxication cases and 20% of the fatalities were caused by TCE (Huang et al. 2002). The largest number of patients to date with the TCE-related generalized skin disorders has been reported there. The first five patients, all females aged 17–22 who later died, were found in a plastic toy company in 1988 (Li et al. 1994). More details about the case occurrence in China are presented in the next section.

1990s: China, Korea, Singapore, Thailand, Philippines, and USA

This decade is characterized by a dramatic increase in the number of reported cases mostly in Asia, i.e. China, Korea, Singapore, Thailand, and the Philippines. The case occurrences in southern China were by far the most remarkable among them. In Guangdong Province, the sixth patient with TCE-related generalized skin disorders was recognized in 1992, and subsequent occurrences were then registered every year thereafter, a total of 45 (36 patients with ED, 3 with EM, and 6 with SJS/TEN) between 1988 and 1998 including 14 fatalities (Li et al. 1998). The Hospital of Occupational Diseases Control of Guangdong Province treated 61 patients suffering from the disorders between April 1997 and December 2000. Of the 61, 50 patients did not receive medications within 4 weeks of disease onset, and had histories of exposure to TCE but not to the other toxicants. They were 26 males and 24 females aged 15–40 (22 years old on average). Forty-four (88%) were Han Chinese, and six belonged to minority groups. Forty cases (80%) were diagnosed as ED, 7 (14%) as EM, two as SJS, and one as TEN. Forty-seven (94%) showed abnormal liver function. All of the patients had inhaled TCE, and the exposure concentrations ranged from 0.3 to 4,085 mg/m^3 (0.1–756 ppm). Thirty-eight had skin contact with the liquid solvent. They worked 10 h a day on average (range 8–14), and the mean duration of exposure before the disease onset was 34 days (range 3–73). The TCE used by the patients was reportedly made in Japan, France, England, and Singapore, and its purity was more than 90% (Xia et al. 2004).

In Taiwan, between July 1996 and January 1997, 57 female Filipino migrant workers suffered from the disorders, and five of them died. The Department of Health of the Government, and the Occupational Safety and Health Center of the Philippines made great efforts to identify the cause. The patients' symptoms and signs were fever, generalized EM, mucosal lesions, and hepatitis. Hepatomegaly, splenomegaly, bronchitis, cervical lymphadenopathy, eosinophilia (5–25%), elevated IgG, IgA, and IgE were also observed. Antibody titers for hepatitis A, B, and C viruses were all negative. The time from beginning work until disease onset was 3 weeks, and the patients were diagnosed as SJS. Forty-six of 57 cases worked in two factories belonging to a company producing computer displays. There were 401 and 544 workers, respectively, in each factory. Many of the patients worked on a display parts assembly line in one factory, or an inspection and repair line for displays in another. No information

was available on what chemicals the patients were exposed to, though the possible candidates were formaldehyde, TCE, copper sulfate, toluene, xylene, tetrachloroethylene, ethyl acetate, and isopropyl alcohol. The workers lived in dormitories, 10–12 workers per room. The odds ratio of disease occurrence was 6, significantly higher than 1, for those whose roommates had suffered the disease, relative to those whose roommates had not. The positive reaction ratio of a cold agglutination test was 67% (14/21) in the SJS patients, which was significantly higher than that (31%, 84/275) in Taiwanese who were examined on the suspicion of being infected with Mycoplasma pneumoniae. In addition, the frequency of HLA-B62 was 91% (20/22) in the affected Filipino workers, significantly higher than the 18% (11/61) in their nonaffected fellow workers, 3% (1/37) in Taiwanese workers, and 11% (3/27) of Taiwanese hospital employees who treated the patients. Though the cause(s) of the SJS remained unclear (Joson et al. 1998; OSHCP 1998), the above case clearly showed some work-related factor(s), including TCE, predisposing the workers to the disorders.

In Korea, at least two cases were recognized by researchers during the 1990s. One was a 25-year-old male who showed rash, oral erosion, subsequent difficulty in swallowing, generalized vesicles with exfoliation, and acute hepatitis in 1995 after 1-month employment in a factory plating a zinc product with nickel. TCE was one of the chemicals used there, but the exposure concentration was unknown. His fellow worker was also hospitalized for similar symptoms at nearly the same time, but the details were unknown (Kang et al. 1999). Another case was a 28-year-old male who degreased copper pipes with TCE about 13 h per week. In 1999, 27 days after beginning work, he showed a fever, generalized erythematous maculopapular rash with itch, edematous purpura in the lower extremities, a marked elevation in his liver enzyme with cholestasis, and elevated IgE (1,414 IU/ml). Histopathological findings were spongiosis of epidermis with lymphocyte infiltration, and edema of dermis with perivascular inflammatory cell infiltration. The rash developed into generalized desquamation after about 1 week. Skin patch test was positive for 0.25% or more TCE in olive oil. He had a drunken feeling after work, felt occasional nausea, and the record of environmental measurement conducted in the previous year revealed the airborne TCE concentration of his worksite to be 853 mg/m^3 (158 ppm). One of his colleagues also reportedly experienced similar symptoms in 1998, but the details are unknown (Chae et al. 2003). The clinical findings of this patient were in accordance with HS.

In Singapore, Tan et al. (1997) reported that a 24-year-old male exposed to TCE at his degreasing job suffered from hepatic encephalopathy and generalized erythroderma that developed into TEN.

In Thailand, the first reported case was an 18-year-old female who had sprayed TCE for about 2 months to clean dirty spots on socks without any exposure protection in a socks-manufacturing factory. She suffered a high fever and an erythematous maculopapular rash developing into generalized hyperpigmentation with residual desquamation on her face, trunk, and extremities, especially on her palms and soles (Chittasobhaktra et al. 1997). These findings also correspond to HS.

In the Philippines, three patients suffered from a generalized cutaneous disorder in 1997, followed by four patients in 1998 (totally five males and two females) in a factory where all 171 employees made ceramic capacitors in an area where TCE was used to degrease capacitor parts. Two patients died. TCA concentrations in the urine of 15 colleagues measured later were 8.2–51.4 mg/l. The measured TCE concentration in the air at a workroom site was 491 mg/m^3 (91 ppm) at most, but the personal exposure concentration of one fellow worker was 1,220 mg/m^3 (226 ppm). After replacing TCE with an alternative solvent, no more workers became ill with these disorders (Estrella-Gust et al. 1999; Hisanaga et al. 2002; Kang et al. 1999).

In Japan, no case report has been published on such disorders since the 1990s. Thus, we conducted a nationwide survey in December 2000 (data not published). A questionnaire was sent to all professors of dermatology (80 recipients with a 69% response ratio), internal medicine ($n = 302$, 36%), ophthalmology ($n = 85$, 44%), occupational and environmental health or public health ($n = 154$, 32%) in medical schools nationwide, asking if they had treated/heard of patients with skin disorders, especially EM/SJS/TEN, in connection with exposure to solvents. No professors reported the solvent-associated generalized skin disorders, except for one case of scleroderma developing after exposure to TCE for 5 months. Thus, this survey result suggests that TCE-associated severe generalized skin disorders resembling drug hypersensitivity either do not occur, or are at least not recognized as a significant clinical issue in Japan today.

Outside Asia, only one case had been reported since the 1990s. Bond (1996) reported a male working in the United States for few weeks as a degreaser without wearing any respiratory protection and consequently suffering weakness, decreased appetite, nausea, abdominal pain, diarrhea, fever, chills, dry skin, red rash with bumps, peeling face, and itching.

Laboratory data showed eosinophilia and marked hepatic enzyme elevation without evidence of involvement of Hepatitis A, B, and C viruses, HIV1, or cytomegalovirus. The patient experienced a recurrence of rash with tremendous itching just after returning to work (Bond 1996).

After 2000: China, Singapore, and Thailand

The patient occurrences have been confined to a few Asian countries in recent years.

In China, a noteworthy new trend is that cases have occurred outside of Guangdong Province: two patients in Guangxi Province (Hu et al. 2003), eight patients in Tianjin [worksite TCE concentration 71–756 mg/m^3 (13–140 ppm)] (Shi and Ma 2005; Wang et al. 2004), and one patient in Beijing (Wang and Yu 2005). However, the number of reported patients is by far the most in Guangdong despite extensive efforts by the local agency and Hospital for Occupational Diseases Control of Guangdong Province to educate both employers and employees with regard to reducing exposure and early detection of the disorders. Dai et al. (2004) collected 111 cases with the disorder occurring in about 80 factories making electronic components or involved in metal plating between May 1999 and November 2003. Their case control study to explore the associations of gene polymorphisms of cytokines with the disorders revealed that individuals with a heterozygous genotype of tumor necrosis factor α-308 were significantly associated with the decreased risk of the disorders relative to the homozygous genotype. The authors mentioned TCE exposure concentrations ranging from 373 to 4,266 mg/m^3 (69–790 ppm) (Dai et al. 2004).

In Singapore, there has been only one case report (Goon et al. 2001) since 2000. A 36-year-old male worked just 5 m away from a degreasing machine at a factory producing car air conditioner compressors for 1 month. He then had generalized erythematous maculopapular rash developing into a confluent dusky erythematous rash with exfoliation. There were mucosal lesions and hepatic dysfunction. A skin biopsy revealed subepidermal clefting and bulla formation, with necrotic keratinocytes in the middle and lower epidermis, along with vacuolar degeneration in the basal layer. There was an infiltrate of lymphocytes in the upper dermis and perivascular area. The urinary TCA level determined 2 weeks after his last day at work was 32 mg/l. The urinary TCA levels of three healthy workers who had worked near the patient were found to be 148.2, 122.0, and 80.1 mg/l, respectively. The authors finally diagnosed the patient as TCE HS.

In Thailand, two cases were reported in 2004 (Pantucharoensri et al. 2004). A 24-year-old woman, employed as a metal strap polisher along with about 130 fellow employees, developed an erythematous rash all over her body, together with edema of both eyelids, fever, and hepatomegaly after working for 5 weeks under TCE exposure. Her urinary TCA concentration was 0.048 mg/l about 2 weeks after quitting her job. Nine days after she experienced the disease onset, another metal strap polisher at the same site, a 23-year-old female, also became feverish and had erythematous macuropapules, which developed later into scaling, with oral involvement. TCA in the urine 4 days after cessation of exposure was 0.8185 mg/l. Working environment measurements conducted 1 month after the onset of the disease revealed airborne TCE concentrations of 81–216 mg/m^3 (15–40 ppm). The factory had operated for more than a decade, but there had never been any similar cases until then (Pantucharoensri et al. 2004).

Relationship between TCE exposures and generalized skin disorders

As shown above, the reported patients were engaged mostly in degreasing, i.e. cleaning metal-made products or machines (Bauer and Rabens 1974; Bond 1996; Chae et al. 2003; Conde-Salazar et al. 1983; Goh and Ng 1988; Goon et al. 2001; Hisanaga et al. 2002; Hu et al. 2003; Kubota 1966; Pantucharoensri et al. 2004; Phoon et al. 1984; Shi and Ma 2005; Tateishi et al. 1969; Wang et al. 2004; Xia et al. 2004), plastic toys (Li et al. 1994), electronics parts (e.g. printed circuit boards, transistor components, capacitors, or computer displays) (Estrella-Gust et al. 1999; Hisanaga et al. 2002; Phoon et al. 1984; Xia et al. 2004), ceramic pieces (Phoon et al. 1984), socks (Chittasobhaktra et al. 1997), ink stains in a printing shop (Nakayama et al. 1988), or unspecified material (Tan et al. 1997; Wang and Yu 2005).

The duration of exposure until the occurrence of the disorders was 3–73 days (Xia et al. 2004) except for two mild cases whose duration of exposure was a year or over (Conde-Salazar et al. 1983; Goh and Ng 1988). Some experienced recurrences after going back to their worksites (Bond 1996; Conde-Salazar et al. 1983; Goh and Ng 1988; Kubota 1966; Phoon et al. 1984). These findings indicate a clear temporal relationship between TCE exposure and the disorder occurrence.

Trichloroethylene exposure concentrations of the patients were available in some of the case reports

(Fig. 2). Environmental measuring results, urinary TCA concentrations of the patients measured during hospitalization, airborne exposure concentrations of their colleagues, and their subjective symptoms suggest that many of the cases were exposed to higher concentrations than the standard, a threshold limit value expressed as a time-weighted average [270 mg/m^3 (50 ppm)] recommended by the American Conference of Governmental Industrial Hygienists (ACGIH 2005) or an Occupational Exposure Limit [135 mg/m^3 (25 ppm)] by the Japan Society for Occupational Health (JSOH 2005). However, there was a case whose time-weighted average exposure concentration should have been lower judging from the undetectable urinary TCA concentration (Goh and Ng 1988). In this case, the short-term ceiling concentration might have been higher since he had inhaled deeply from a barrel which contained TCE when he suffered skin lesions. Some other authors also reported relatively lower environmental TCE concentrations. However, they were measured after the patient occurrences and were not necessarily the same as those at which the patients were exposed. The true short-term ceiling concentrations as well as time-weighted average concentrations were unclear in many cases.

Cause of TCE-related generalized skin disorders

It remains controversial whether TCE itself or other work-related hazard(s) was a cause of the generalized hypersensitivity reaction. Increase in serum IgE level was reported in some of the patients (Chae et al. 2003; Conde-Salazar et al. 1983; OSHCP 1998; Wang and Yu 2005). Some cases themselves did not use TCE, but worked close to degreasing machine(s) (Goon et al. 2001). This suggests that skin contact with liquid TCE is not essential for the onset of the disorders, and that chemicals not vaporizing under the usual room or degreasing-machine temperature conditions (e.g. metals) are not involved as the causes. The first Thai case whose work was to spray TCE on socks also suggested that solvent itself was the cause of the disorders. However, one must keep in mind that unelucidated work-related factor(s) other than solvent exposure, e.g. infectious disease(s) in the involved workplace, might have played a supplementary role in causing or developing the disorders since more than one patient was sometimes observed in the same workplace at intervals within half a month (Kubota 1966; Pantucharoensri et al. 2004; Phoon et al. 1984; Wang et al. 2004; Shi and Ma 2005).

When discussing the cause of the disorders, one should recall that patient occurrences have been increasing after the 1990s. As shown in Table 1, cases from industrialized countries were reported up to 1990 (except for Bond 1996), whereas cases from Asian developing nations were reported thereafter. There are two possible explanations for this. The first is the increased number of exposed populations not sufficiently protected from occupational exposure to TCE as a result of rapid industrialization. In Guangdong Province, China, a survey in a city demonstrated that 3,000 workers were directly exposed and 40,000 indirectly to TCE at the same time, and it was estimated that at least 20,000 new workers were exposed to TCE every year. In addition, physicians in the city and the surrounding area began to pay more attention to the link between generalized skin disorders and occupational TCE exposure because it was one of the most critical occupational health issues in the area (Huang et al. 2002).

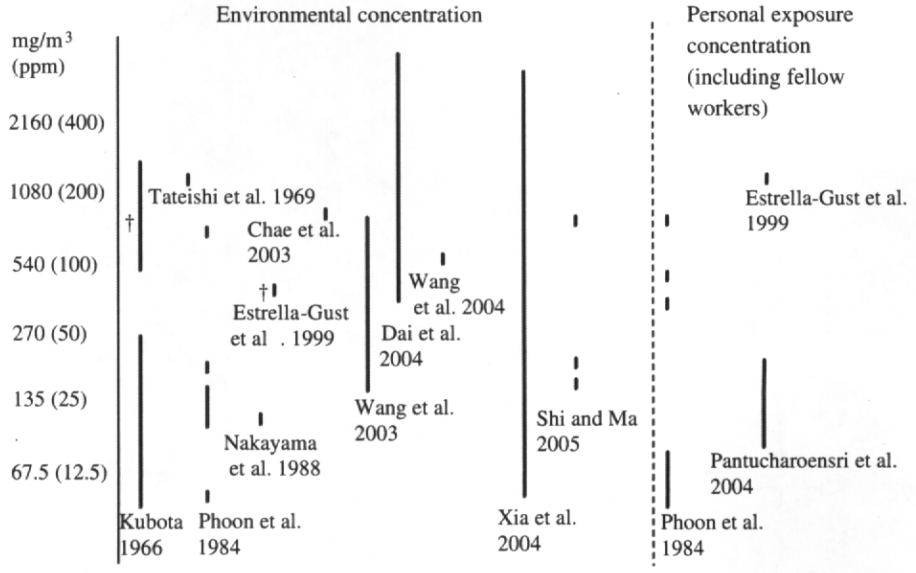

Fig. 2 Environmental trichloroethylene concentrations and time-weighted personal exposure concentrations in the workplaces of patients suffering from generalized skin disorders. †Ceiling concentration

The second possible explanation is that impurities and stabilizers contained in commercially available TCE in the endemic region are different from those in the other countries. 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 (WHO 1985). Stabilizers are added to prevent the solvent breaking down into hydrochloric acid, which can corrode the parts being cleaned and the cleaning equipment itself (Mohr 2001). It is known that skin sensitization can be due to one or more of the stabilizers (Wahlberg and Adams 1999). In this regard, patch test results were described in some of the case reports. However, it was unclear if the tested TCE contained stabilizers or not.

The following are possible impurities detected in commercially available TCE: carbon tetrachloride, chloroform, 1,2-dichloroethane, *trans-* or *cis*-1,2-dichloroethylene, pentachloroethane, 1,1,1,2- or 1,1,2,2-tetrachloroethane, 1,1,1- or 1,1,2-trichloroethane, 1,1-dichloroethylene, bromodichloroethylene, perchloroethylene, bromodichloromethane, and benzene. It is uncommon for any individual impurity to be present at a level in excess of 100 mg/kg (WHO 1985). As for stabilizers, aliphatic amines (e.g. triethylamine, triethanolamine, diisopropylamine), heterocyclic nitrogen compounds (e.g. pyridine, pyrrole, alkyl pyrroles) or substituted phenols (e.g. 2-methoxyphenol, cresol), or oxygenated organics (e.g. 1,4-dioxane, acetone, methyl ethyl ketone, butylene oxide, propylene oxide, tetrahydrofuran, epichlorohydrin) are added at concentrations usually ranging from 20 to 600 mg/kg for the purpose of free radical scavengers, antioxidants, or acid-acceptors, respectively, depending on patent ownership and the technical specifications being met (WHO 1985; Mohr 2001). The presence of these stabilizers cannot be readily discerned from current material safety data sheets except for 1,2-butylene oxide, as the quantities added do not meet the threshold for listing (Mohr 2001). Stabilizers currently produced or in use might be different from those in the past, and between industrialized and industrializing countries. One example is epichlorohydrin, which was mostly replaced with 1,2-butylene oxide until the 1980s (WHO 1985). In addition, used TCE (contaminated with polluting materials) can be made fresh by re-distillation, but needs further addition of stabilizers before re-use. Thus, the stabilizers added to the endemic region might be different from those added originally at the sites of TCE synthesis. In this regard, Huang et al. (2002) reported that the TCEs used in Guangdong where most of the Chinese cases occurred were more than 90% pure, and made in various countries/regions such as Japan, Hong Kong, Great Britain, the USA, and China. They considered that the levels of impurities in these TCEs were different (Huang et al. 2002).

There have been at least two case reports of generalized skin disorders induced by tetrachloroethylene exposure. One case report appeared in Japan in 1979, and the other in China in 1999 (Hisanaga et al. 2002). Tetrachloroethylene is more stable than TCE and requires only small amounts of stabilizers. The possible stabilizers are amines, phenols, cyclohexene oxide, and butoxymethyloxirane (Mohr 2001), some of which may be common to TCE. Once tetrachloroethylene is absorbed into the body, 97–99% is eliminated unchanged via exhalation, and the remainder is oxidized by cytochrome P450 to TCA, the same urinary metabolite as TCE, which is detected in far lesser amounts than when one is exposed to the same concentration of TCE (Waksman and Phillips 2004). In contrast, in the metabolism of TCE, the cytochrome P450 oxidative pathway plays a major role and chloral hydrate is detected as a metabolite (Lash et al. 2000; Nakajima 1997). Chloral hydrate, used as a sedative, could reportedly induce generalized skin eruption. A 36-year-old female suffered generalized erythematous maculopapular exanthema after receiving medication including chloral hydrate for 10 days. Chloral hydrate was confirmed to be the causative agent by patch test and oral provocation test (Lindner and Prater 1990). Arndt and Jick (1976) described the rate of chloral-hydrate-induced skin reaction [any of the following: (1) eruptions characterized by rapid onset and widespread, bilateral involvement with maculopapular erythema, (2) hives, and (3) generalized itching] as 0.02% (one patient out of 4,809). Taken together, it is certain that TCE itself or its metabolite(s) can be the cause of generalized skin disorders. Major common stabilizers introduced after the 1980s, e.g. 1,2-butylene oxide, are also among the candidate chemicals, though there has been no direct evidence to support the possible role of the stabilizers in causing or developing the disorders.

Concluding remarks

Diseases associated with occupational TCE exposure are an ongoing problem in Asian countries today. TCE-related generalized skin disorders are important not only in terms of the number of disease occurrences and their severity but also from the viewpoint of drug hypersensitivity. In order to address the mechanism of the disorders, it is necessary to collect clinical information

by a structured checklist in cases diagnosed by the same criteria as those used for drug hypersensitivities. In addition, detailed exposure assessments are also required to establish preventive strategies in the affected countries.

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