Review

Generalized Skin Reactions in Relation to Trichloroethylene Exposure: A Review from the Viewpoint of Drug-Metabolizing Enzymes

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Abstract: Generalized Skin Reactions in Relation to Trichloroethylene Exposure: A Review from the Viewpoint of Drug-metabolizing Enzymes: Tamie Nakajima, et al. Department of Occupational and Environmental Health, Nagoya University Graduate School of Medicine

The literature was reviewed to study cases of intoxication with systemic dermatitis associated with exposure to trichloroethylene. The average age of patients in the reports reviewed to date was twenty-nine; these diseases were found in relatively young persons and no difference was found according to gender. Many cases occurred within one month after the onset of exposure to trichloroethylene, and were accompanied by hepatitis, jaundice, hepatomegaly or hepatosplenomegaly. Most of the patients had no history of drug abuse or herpes infection. The level of exposure to trichloroethylene was not recorded in many cases, but ranged from less than 9 ppm to 800 ppm. In the severest cases, the lesions involved mucous membranes such as the conjunctiva and oral cavity, and the patients were diagnosed with Stevens-Johnson syndrome, but the etiology of the disease after trichloroethylene exposure remains unclear. Since several drugs have also been shown to cause systemic dermatitis with hepatitis, susceptibility factors are discussed. Many patients were found to have the slow acetylator genotype of N-acetyltransferase (NAT) 2, suggesting that the NAT2 genotype is a susceptibility factor. This hypothesis may also be applicable to trichloroethylene because NAT is involved in the glutathione-mediated metabolism.

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Trichloroethylene is mainly used as a solvent to remove grease from metal parts or lenses, and as a chemical to make other chemicals. Occupational exposure to trichloroethylene is known to cause a variety of health hazards. Together with anesthetic action, hepatic damage, polyneuropathy, trigeminal neuropathy, and dermatitis with skin irritation are familiar diseases which occur as a result of exposure1, 2).

In addition to the non-specific skin irritation resulting by the defatting action, severer generalized dermatitis with hepatitis, which includes Stevens-Johnson syndrome and toxic epidermal necrolysis, sometimes occurs after exposure to trichloroethylene3–10). Such dermatitis is generally known to occur subsequent to the administration of various medicines and infections-i.e., antibiotics such as sulfonamides, anticonvulsives such as carbamazepine and phenobarbital, anti-inflammatory medications such as acetylsalicylic acid and paracetamol, anti-parasitic medications such as albendazole and tinidazole, viruses, mycoplasma, and other bacterial infections11–15). As for other types of chemical exposure, there have been a few case reports on the dermatitis, that of a young woman who used pesticide spray16), and students who were exposed to 9-bromofluorene in a lab setting17). Thus, although many kinds of chemicals have the potential to cause severer generalized dermatitis with hepatitis, trichloroethylene must be one of the most important causative chemicals as shown in an epidemic of the disease in China; an epidemic reported as involving over 100 workers occupationally exposed to trichloroethylene in Guangdong, China, who suffered from dermatitis with hepatitis18).

A review of the literature was performed to study cases of intoxication with systemic dermatitis associated with
exposure to trichloroethylene and tetrachloroethylene. Since almost all of these patients suffered from hepatitis, the possible involvement of the metabolism of trichloroethylene in liver drew our attention. In this review, we discussed the mechanism in relation to the genetic polymorphism of enzymes involved in the trichloroethylene metabolism.

**Clinical manifestation of trichloroethylene-related generalized skin reactions**

The occupational and clinical characteristics of thirteen typical patients who suffered from generalized dermatitis, including Stevens-Johnson syndrome associated with trichloroethylene exposure, are summarized in Table 1. Bauer and Robens first reported four patients who developed generalized dermatitis after exposure to trichloroethylene. All of the patients had been engaged in the cleaning of metals or bomb casings with trichloroethylene, but the time from the use of this particular solvent until the onset of dermatitis was not mentioned. Only one patient (case 3) had developed hepatitis, as determined by increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and bilirubin levels.

<table>
<thead>
<tr>
<th>Table 1. Occupational background and clinical findings of patients with generalized dermatitis after exposure to trichloroethylene</th>
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<tbody>
<tr>
<td>Patients</td>
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<tr>
<td>Age (yr)</td>
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<td>Sex</td>
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<td>Type of business</td>
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<td>Occupation</td>
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<td>Period from TRI use to the onset of dermatitis</td>
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<td>Workers in the same workplace (n)</td>
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<td>Mucous lesions</td>
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<td>ALT (IU/l)</td>
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<td>ALP (IU/l)</td>
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<tr>
<td>Total bilirubin (µmol/l)</td>
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<td>Hepatomegaly</td>
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<td>Eosinophilia</td>
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<td>Patch tests</td>
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<td>Environmental concentration of trichloroethylene (ppm)</td>
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<td>Herpes infection</td>
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<td>Drug abuse or medication before disease onset</td>
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Phoon et al. reported five cases. Cases 5 and 6 were twin sisters who had worked in the same factory. Case 5 used trichloroethylene to remove epoxy resins from transistor parts, and case 6 checked the cleaned parts and occasionally assisted case 5 in her work. Three weeks after commencing work, fever appeared in case 5 and three days later, in case 6, and multiform exudative erythema was also observed on the face, arms and mouth in both cases. Their ALT levels were high, and hepatomegaly was observed. Neither had a history of drug use or herpes infection. Cases 7 and 9 worked in the same condenser manufacturing plant, using trichloroethylene to clean ceramics and equipment products. The concentration in the workplace was between 40 and 169 ppm. Five wk after case 7 began work and two wk after case 9 did so, multiform exudative erythema was observed on the body and around the lips. Biochemical findings for both cases were equivocal, but liver dysfunction and hepatomegaly were presumably observed. Neither case had a history of drug use or of previous herpes simplex infection. Case 8 worked at a factory where metal parts such as bearings and rollers...
were manufactured. He alloyed metals, and wrapped the products manufactured. Although this patient had no direct exposure to trichloroethylene in the workplace, a tank of trichloroethylene was found in the room where he worked. Therefore, his trichloroethylene exposure level was thought to be relatively low. Three wk after beginning work, systemic erythema, liver dysfunction, hepatomegaly, and jaundice appeared in this patient. Thirteen wk after his condition had improved for the first time, his erythema and liver dysfunction reappeared after exposure to trichloroethylene at his workplace. This particular patient refused hospitalization, and returned to work two days later, but his symptoms increased to include hepatosplenomegaly, as well as exfoliative dermatitis, the following week. He continued going to work, but died fourteen days later.

Nakayama et al. reported a patient intoxicated by the use of trichloroethylene as a degreasing agent. Two wk after commencing work, systemic erythema and liver dysfunction with high fever were observed in this patient. Patch tests for trichloroethylene and trichloroethanol turned up positive, but exposure levels at the workplace were unknown. Schattner and Malnick also reported the case of a female with dermatitis concomitant with hepatitis. She had been cleaning machine parts with trichloroethylene at work. This male patient refused hospitalization, and returned to work two days later, but his symptoms increased to include hepatosplenomegaly, as well as exfoliative dermatitis, the following week. He continued going to work, but died fourteen days later.

Bonfret et al. reported the case of a thirty-year-old man who used trichloroethylene as part of a degreasing process (case 12 in Table 1). The patient had no underlying illness, but began to complain a few weeks after commencing work of weakness, dizziness, loss of appetite, nausea, abdominal pain, diarrhea, fever, chills, eczema, peeling face and itchiness. He had high ALT values (1,250 IU/l), and showed an increase in atypical lymphocytes. This male patient was exposed to a level of trichloroethylene that caused a symptom called degreaser’s flush. His history of alcohol use was determined to be one or two bottles of beer on weekdays, and four or five bottles of beer on his days off. After two wk, his ALT values decreased from 1,250 IU/l to 717 IU/l. He tested negative for hepatitis viruses A, B and C, as well as for HIV and cytomegalovirus.

On the night of the day he recommenced using trichloroethylene at work, he experienced a recurrence of systemic diffuse erythema concomitant with a severe itch. In spite of not drinking any alcohol, the erythema spread. This patient took a few days off from work, but the erythema continued and began to scale. Even after one wk, the erythema scaling and edema continued. His ALT level was 517 IU/l, and his leukocyte count was 10,100/mm³; 27% of his leukocytes were eosinophilic.

Chittasobhakta et al. reported the case of an eighteen-year-old woman who used trichloroethylene as a cleaning agent at a sock factory (case 13 in Table 1). She had no underlying illness, and no history of blood transfusion or of drug or alcohol abuse. Approximately one month after beginning work, she began to have fevers, erythema and jaundice, and she experienced nausea and vomiting. When she visited a regular hospital, the doctor described her as having mild jaundice, hepatomegaly, and erythema on the face, trunk, and extremities. She was treated for salmonella infection, but no improvement was seen. She was then transferred to the hospital where one of the authors of the study was on the medical stuff. In addition to the symptoms mentioned above, there was enlargement of the cervical lymph nodes. Liver function tests indicated AST levels of 115 IU/l, ALT levels of 56 IU/l, alkaline phosphatase (ALP) levels of 113IU/l, albumin at 38.8 mg/l, and total protein at 61.1 mg/l. Tests for the hepatitis A, B and C viruses, rickettsial diseases, melioidosis and HIV were negative. A biopsy of the left cervical lymph node indicated hyperplasia. In a liver biopsy, thickened liver cell cords, the appearance of multinucleated giant liver cells, liver cell necrosis in the centrilobular zone caused by invasion of polymorphonuclear leukocytes, and lymphocytic infiltration in the portal vessel, similar to findings seen with chronic hepatitis, were observed. Patch tests were performed to examine allergic responses to trichloroethylene and trichloroacetic acid, but she showed only a positive reaction to 50% trichloroethylene. The patient’s liver functions returned to normal within three months after she was first admitted to the hospital.

As shown in Table 1, in many cases symptoms developed within a month after beginning to use trichloroethylene. Jaundice was observed and hepatomegaly was noted in many cases. Most patients had no history of drug use or herpes infection. The levels of exposure to trichloroethylene in the majority of cases were unclear, but ranged from less than 9 ppm to 800 ppm when measured. It should be noted that symptom development started at an exposure level of 9 ppm or lower. There was no difference according to gender, and all cases appeared in relatively young persons.

Trichloroethylene and the developmental mechanism of generalized skin reactions and associated liver dysfunction

Trichloroethylene is mainly metabolized by cytochrome P450 (CYP) to chloral hydrate, which is further converted by alcohol (ADH) and aldehyde dehydrogenases (ALDH) to trichloroethanol and trichloroacetic acid, respectively. Most of the trichloroethanol is conjugated with UDP-glucuronyltransferase to form urocholar acid, some of which is converted by microsomal alcohol oxidation enzyme to trichloroacetic acid via chloral hydrate. Of CYP isozymes, CYP2E1 is a major form in the metabolism either in rodents or human, and also plays an important role in trichloroethylene-induced
hepatic damage\textsuperscript{22, 23}. Another metabolic pathway of trichloroethylene is a glutathione-mediated metabolism by glutathione S-transferase: relatively small amounts of trichloroethylene are conjugated with GSH to form S-(1, 2-dichlorovinyl) glutathione (DCVG)\textsuperscript{24}. DCVG is further converted to S-(1, 2-dichlorovinyl)-L-cystein (DCVC) by \( \gamma \)-glutamyltransferase and dipeptidase. The DCVC formed is acetylated to N-acetyl-S-(1, 2-dichlorovinyl)-L-cystein by N-acetyltransferase, or is converted to pyruvic acid, ammonia and reactive thiols by \( \beta \)-lyase. It is generally thought that trichloroethylene is detoxicated or bioactivated through the former and the latter step, respectively.

Patients who develop generalized skin reactions may be sensitive to trichloroethylene or its metabolites. A patch test was performed with a 5\% tincture of trichloroethylene in olive oil on patient 7, and a negative result was observed. Patch tests for trichloroethylene, trichloroethanol, and trichloroacetic acid were performed on patient 10. A weak positive response was found for trichloroethylene levels at 10 and 25\%, but at the 5\% level, a negative result was observed. A medium positive result was seen when using 0.005–5\% trichloroethanol, but at 5\% trichloroacetic acid, a negative result was observed. In two cases (cases 10 and 13), the trichloroacetic acid patch tests returned negative results, making it difficult to identify trichloroacetic acid as a cause. Considering the weak positive at high levels of trichloroethylene, and only one positive response at a low level of trichloroethanol, the cause appears to lie with the trichloroethanol itself or the metabolite(s). It may be possible to determine the cause(s) of the disease by using patch tests of trichloroethylene or its metabolites; but, considering that patient 8 died after repeated exposure to trichloroethylene, caution is necessary when deciding to perform such tests.

It remains unclear how trichloroethylene causes generalized skin reactions and the associated liver dysfunction. Trichloroethylene inhibits the activity of ALDH and the metabolism of low-molecular-weight aldehyde with short carbon chains\textsuperscript{25}. Therefore, aldehydes may easily accumulate in the body after exposure to trichloroethylene. Since degreaser’s flush occurred after alcohol consumption in case 12, occupational exposure to trichloroethylene might have blocked ALDH (in particular, ALDH2, which has an affinity for acetaldehyde). This led to the hypothesis that this blockage of ALDH might be the trigger for the generalized skin reactions. It is still unclear whether many of the possibly causative agents block ALDH.

No serious liver damage was observed in either rats exposed to high levels of trichloroethylene or rats with prolonged exposure\textsuperscript{22, 23}. If, however, CYP isozymes (CYP2B1/2 and CYP2E1, respectively) were induced when using phenobarbital or alcohol, AST and ALT levels became increased to about 10,000 IU/l after exposure to high levels of trichloroethylene, and serious liver damage was observed. But no similar results were observed when using chloral hydrate. These results indicate that any intermediate metabolites between trichloroethylene and chloral hydrate may cause serious liver damage related to trichloroethylene, but it is unclear whether skin damage, such as erythema, was observed in the rats used in the study. If we consider these results in light of the observation that a patch test for trichloroethanol was positive in patient 10, involvement of CYPs in the disease with trichloroethylene exposure seems to be unlikely.

**Polymorphism of drug-metabolizing enzymes and generalized skin reactions induced by various chemicals**

Some studies have assumed a genetic link to the cause of drug-induced generalized skin reactions. Green et al.\textsuperscript{26} studied the relation between high sensitivity to carbamazepine and epoxide hydrolase (EH) genetic polymorphism based on the findings that 1) the cellular toxicity of carbamazepine is neutralized by EH, 2) metabolized carbamazepine epoxide is neutralized by glutathione S-transferase (GST) and/or EH, 3) in epidemiological studies, an increased incidence of fetal disorder was observed in pregnant women to whom sodium valproate, an inhibitor of EH, was administered, and 4) there is an inverse correlation in animal experiments between EH levels and fetal disorder caused by phenitoin, which induces the same side effects as carbamazepine. DNA was extracted from a control group of ten healthy individuals and from ten patients suggestive of hypersensitivity to carbamazepine (toxic epidermal necrolysis, Stevens-Johnson syndrome, hepatitis and pneumonitis; all cases exhibited skin reactions). PCR-SSCP was used to perform the screening for nine exon variations within the EH gene, and the variations identified were analyzed directly by sequence analysis. A higher frequency of variation was observed in the patient group than in the control group, but the results were inconsistent. In the most serious case, the EH gene was a wild type gene. In addition to the difficulty in drawing conclusions based on a study of only ten persons, only one variation in the coding region of the EH gene may be insufficient to serve as a predictor for sensitivity to carbamazepine. As for the trichloroethylene metabolism, the contribution of EH must lie somewhere between trichloroethylene and chloral hydrate. If the causative metabolite is to be trichloroethanol or the metabolite(s), it would as yet be difficult to pinpoint the polymorphism of the EH gene as a factor.

Acetylation catalyzed by \( N \)-acetyltransferase (NAT) is the major route of conjugation reaction of many xenobiotics. The two genes (\( NAT1 \) and \( NAT2 \)) that encode
NATs have been sequenced\(^\text{27}\). \(\text{NAT1}\) is polymorphically distributed in humans, and individuals that inherit rapid \(\text{NAT1}\) are at a high risk of bladder cancer\(^\text{28}\). Independently of this, \(\text{NAT2}\) exhibits a polymorphism due to a point mutation in the coding region, and individuals possessing it can be designated as phenotypically slow or fast metabolizers\(^\text{29}\). Rapid acetylators are either heterozygous or homozygous for wild-type alleles of \(\text{NAT2}\). Slow acetylators that carry \(\text{NAT2}\) mutant alleles produce proteins that are either poorly expressed, unstable, or have partially reduced catalytic activities.

Patients with generalized skin reactions due to drugs which are metabolized by NAT may have had a greater frequency of the slow type of NAT2 than the control group. Wolkenstein et al.\(^\text{30}\) explored the relation between Stevens-Johnson syndrome or a toxic epidermal reaction associated with either sulfonamide or anticonvulsive drugs, such as carbamazepine and phenobarbital and a genetic polymorphism for NAT2 and GSTM1. Patients without HIV (18 from among groups associated with sulfonamide, and 14 from among groups associated with anticonvulsive drugs) were studied, along with 20 healthy individuals of the same age, who were included in a control group. DNA was extracted from the peripheral leukocytes, and analyses were performed for polymorphism in both groups. Seventeen of the 18 patients with sulfonamide-related Stevens-Johnson syndrome were demonstrated as having the slow type of NAT2; this showed a clearly higher frequency than that of the control group, where this type of NAT2 was demonstrated in only ten out of twenty individuals. Of the fourteen patients with anticonvulsive-related Stevens-Johnson syndrome, eight had the slow type of NAT2, showing no difference from the control group. For the GSTM1 gene, there was no difference in the frequency of the defective type of gene between the patients with sulfonamide or anticonvulsive drug-related Stevens-Johnson syndrome and the control group. Therefore, the genotype of the acetylator may be one of the susceptibility factors in Stevens-Johnson syndrome and in other toxic epidermal reactions associated with sulfonamide.

Dietrich et al.\(^\text{11}\) investigated the correlation between Stevens-Johnson syndrome, toxic epidermal reaction, and the activity of NAT with regard to various drugs. Cells were extracted from the hair roots (10–15, respectively) of nine persons with Stevens-Johnson syndrome, and six persons with either a complex of Stevens-Johnson syndrome and toxic epidermal reaction or toxic epidermal reaction alone (nine white females, six white males, drugs were not specified). Cell roots were also extracted from 34 healthy white individuals (20 females and 14 males); 2-aminofluorene was used as a substrate to evaluate acetyl-CoA-dependent N-acetylation by HPLC. The activity for the patient group was 0.85 nmol/mg/min, slightly lower than the value of 2.21 nmol/mg/min observed in the control group. A good correlation between the activity of NAT in the hair roots and that in the liver was demonstrated by caffeine tolerance, allowing us to conclude that NAT activity in the patients’ livers was lower than that in the controls, and that all patients had the slow-type phenotype of NAT. In comparison, 58% of the control group had the slow type of NAT. Therefore, the NAT2 genotype is considered to be a factor in susceptibility to serious adverse skin reactions associated with certain drugs.

NAT2 is also involved in the glutathione-mediated metabolism of trichloroethylene. Very recently, relationships between trichloroethylene-induced generalized skin reaction and genetic polymorphisms of NAT2 as well as other drug-metabolizing enzymes CYP1A1, GSTM1, GSTP1, and GSTT1 were investigated in 43 patients and 47 healthy workers exposed to trichloroethylene by Huang et al.\(^\text{18}\). Of these enzyme polymorphisms, only NAT2 slow genotype significantly increased the risk of trichloroethylene-induced dermatitis. Unfortunately, CYP2E1 and UDP-glucuronontransferase polymorphisms were not involved in the study. Furthermore, it is unclear whether it is involved in the trichloroethanol metabolism. Therefore, if trichloroethanol is responsible for trichloroethylethene-associated generalized skin reactions, it might be necessary to demonstrate a correlation between trichloroethanol and NAT.

In conclusion, genetic polymorphism for NAT2 may be a factor that increases susceptibility to trichloroethylene-induced generalized skin reactions. But, in all cases, the research was limited by the use of small groups; therefore, epidemiological studies of large populations are still needed.

**References**

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