Two Sensitive Sick-building Syndrome Patients Possibly Responding to *p*-Dichlorobenzene and 2-Ethyl-1-Hexanol: Case Report

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Sick-building syndrome (SBS) symptoms associated with indoor air volatile organic compounds (VOCs) in new or newly remodeled houses have been increasingly highlighted, and are known as "sick house syndrome" in Japan. In the course of the investigation of SBS patients, we found two sensitive patients who complained of severe symptoms and had elevated serum levels of *p*-dichlorobenzene and 2-ethyl-1-hexanol. One patient was a housewife, who complained of various symptoms such as headache, itching eyes, nasal irritation, and night sweats and had a high serum level of *p*-dichlorobenzene (25.4 ng/ml). She showed some improvement of symptoms in association with the gradual decrease in *p*-dichlorobenzene concentrations in both her bedroom and her serum. The other patient was a female professor who had experienced mainly respiratory symptoms, such as nonproductive cough, throat irritation, *etc*. when she entered her office, classrooms, and a faculty meeting room in a university building. Her serum 2-ethyl-1-hexanol concentration was 4.6 ng/ml, which was more than 7.7-fold higher than that in four other patients with other onsets. The elevation of her serum 2-ethyl-1-hexanol level was assumed to be due to daily exposure in the university building.

Key words—— sick building syndrome, *p*-dichlorobenzene, 2-ethyl-1-hexanol, volatile organic compounds, serum

INTRODUCTION

Sick-building syndrome (SBS) has become a serious problem in indoor environments, in homes as well as in workplaces.[1)] Volatile organic compounds (VOCs) pose possible health risks that could result from exposure to indoor airborne VOCs as suggested by the causal associations with symptoms of SBS.[2)] There is no universally accepted clinical definition of SBS and no adequate theory for its occurrence.[1)] The complaints are usually nonspecific, such as headache, nausea, irritated eyes, cough, dry and itchy skin, *etc*. For most people, the health problems disappear when leaving the building. In Japan, SBS symptoms associated with indoor air VOCs in new or newly remodeled houses have been increasingly highlighted, and are known as "sick house syndrome."[3)] The Ministry of Health, Labour and Welfare of Japan provided guideline values (GLV) for indoor concentrations of 13 VOCs, such as formaldehyde, toluene, *p*-dichlorobenzene, *etc*., and promulgated an advisable value of total VOCs.[4)]

Although past research tried to understand the causes of SBS, it did not generally succeed in showing direct evidence that elucidates the relationship between SBS and VOCs.[2)] Recently, Saijo *et al*. reported that indoor air concentrations of some VOCs were significantly related to the symptoms, and the sum of all VOCs was significantly related to throat and respiratory symptoms, although the concentrations of VOCs were relatively low.[5)] However, to our knowledge, no study on the relationship between SBS and serum VOC concentrations has been conducted. To address this issue, we measured serum VOC concentrations in patients and volunteer controls; however, it was difficult to identify the responsible VOCs and their serum levels inducing the SBS symptoms because we did not find statis-

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tically significant differences in the concentrations of studied VOCs between the patients and controls and also found no relationship between serum VOC levels and SBS symptoms in the patients studied.[6] In the course of the investigation of SBS patients, we found two sensitive patients who complained of severe symptoms. In this study, we intended to examine the relationship between exposure to VOCs and SBS symptoms in the two patients by measuring serum and indoor air VOC concentrations.

PATIENTS AND METHODS

Patients —— Patient A was a 44-year-old housewife from Sapporo, Japan. She complained of various symptoms such as headache, itching eyes, nasal irritation, night sweats, *etc*. Patient B was a 61-year-old female professor of Foreign Culture and Literature from Nagoya, Japan. She had been experiencing mainly respiratory symptoms, such as nonproductive cough, throat irritation, *etc*. when she entered her office, classrooms, and a faculty meeting room in a university building. 2-Ethyl-1-hexanol was suspected of being responsible for her respiratory symptoms because the indoor air concentrations of 2-ethyl-1-hexanol in the university building in summer were very high (max: approximately 1000 $\mu g/m^3$),[7] a level beyond the advisable value of total VOCs (400 $\mu g/m^3$).[4] Four other patients had other onsets such as moving into a new or newly remodeled house.

Measurement of VOCs in Serum —— For the measurement of VOCs in serum, 1 ml of serum was diluted with 14 ml of saturated saline solution and analyzed using headspace GC/MS.[6] VOCs were quantified using deuterated compounds as internal standards. Target VOCs were benzene, toluene, xylene, ethylbenzene, styrene, *p*-dichlorobenzene, and 2-ethyl-1-hexanol. HS-GC/MS analysis was carried out under the following conditions: headspace sampler, Tekmar 7000 (Tekmar, Mason, OH, U.S.A.); vial size, 22 ml; sample temperature, 60°C; sample equilibrium time, 20 min; mixer, on (power 5, 3 min); sample loop size, 1 ml; sample loop temperature, 150°C; and transfer line temperature, 160°C. GC/MS, Auto Mass System II (Jeol, Tokyo, Japan); column, Vocol (60 m × 0.25 mm *i.d.*, 0.1 μm film thickness, Supelco, Bellefonte, PA, U.S.A.); oven temperature, initial temperature 40°C with 4-min hold, then 10°C/min to 230°C and postrun at 230°C for 5 min; ion source temperature, 210°C; and electron ionization voltage, 70 eV.

Measurement of VOCs in Indoor and Breathing-zone Air —— For the measurement of VOCs in indoor and breathing-zone air, both active and passive sampling was used. Active sampling was carried out using personal pumps (PAS-500, Shibata Scientific Technology, Tokyo, Japan) attached to charcoal tubes (gas tube for organic solvents, Shibata Scientific Technology) with an air sampling rate of 100 ml/min. Passive sampling was carried out using a passive gas tube (Shibata Scientific Technology) or VOC-SD (Supelco, U.S.A.). Both active and passive sampling continued for 24 hr. The collected VOCs were extracted with carbon disulfide and analyzed using GC/MS, which was carried out under the following conditions: QP-5050A (Shimadzu, Kyoto, Japan); column, DB-1 (60 m × 0.25 mm *i.d.*, 1.0 μm film thickness, J&W Scientific, Santa Clara, CA, U.S.A.); oven temperature, hold at 40°C for 5 min, ramp at 10°C/min to 150°C, ramp at 20°C/min to 250°C, and hold at 250°C for 18 min; injector temperature, 250°C; and detector temperature, 280°C. Analysis was performed in a selected-ion monitoring mode.

Ethics —— This study was carried out as a part of the treatment of patients and was conducted according to the Declaration of Helsinki; signed informed consent was obtained from the patients.

RESULTS AND DISCUSSION

Case 1

The study design for patient A included a five-point series of measuring serum and/or indoor air VOCs and two types of countermeasures (Table 1). At time point 1, her serum level of *p*-dichlorobenzene (25.4 ng/ml) was high, but those of eight other VOCs (not detected 0.4 ng/ml) were low. We informed her of the results and conducted a follow-up investigation together with measures to reduce exposure to *p*-dichlorobenzene. At time point 2, the indoor air level of *p*-dichlorobenzene (0.35 ppm) was high, 8.8-fold higher than the GLV (0.04 ppm), while those of five other VOCs such as toluene and xylene were low (<0.001–0.004 ppm). As the first countermeasure, mothballs, which are *p*-dichlorobenzene products, were removed from drawers in her bedroom and ventilation of the living room and her bedroom was carried out as frequently

Table 1. Serum and Indoor Air Concentrations of *p*-Dichlorobenzene Sampled from Patient A

Time point	Date	Concentration	
		Serum (ng/ml)	Indoor air (ppm)[a)]
1	January 2002	25.4	—[b)]
2	May 2002	—[b)]	0.35
3	September 2002	8.0	0.10
4	December 2002	12.0	0.036
5	June 2003	19.3	0.008

a) Samples were collected in the bedroom. *b*) Not measured.

as possible. At time point 3, the concentrations of *p*-dichlorobenzene in her serum and her bedroom decreased to 8.0 ng/ml and 0.10 ppm, levels 1/3.2 and 1/3.5 of those at time point 2, respectively. Some improvement in her symptoms was observed at time point 3. The concentration of *p*-dichlorobenzene in her bedroom still exceeded the GLV at that time.

As further countermeasures, clothes in drawers were aired together with facilitating the ventilation of the living room and her bedroom. At time point 4, the concentration of *p*-dichlorobenzene in her bedroom decreased to 0.036 ppm, a level 1/2.8 of that at time point 3, and less than the GLV, whereas the serum level was 12.0 ng/ml, 1.5-fold higher than at time point 3. Recovery continued at time point 4. At time point 5, she reported a relapse. The concentration of *p*-dichlorobenzene in her serum again increased to 19.3 ng/ml, although that in her bedroom decreased to 0.008 ppm. It became apparent that she had frequently visited a friend's house to babysit for 2 or 3 months before time point 5. When she entered the house, she always developed a headache due to the strong odor. The elevation of serum *p*-dichlorobenzene level was presumably caused by exposure at the friend's house. We advised her not to enter the house.

As *p*-dichlorobenzene is used widely in moth repellent, air fresheners, and deodorizers, elevated serum *p*-dichlorobenzene levels may be caused by the common use of these products. The excretion of *p*-dichlorobenzene may be slower than that of other VOCs, such as toluene, xylene, *etc*. At time point 4, the serum *p*-dichlorobenzene level was still high (12.0 ng/ml) although the level of *p*-dichlorobenzene in her bedroom was greatly decreased (from 0.35 to 0.036 ppm). One of the reasons for the elevation of her serum *p*-dichlorobenzene level is that she may be a poor metabolizer. Additionally, she was suspected of having multiple chemical sensitivity because her condition was unstable due to the occasional and accidental exposure to nonspecific odors. Multiple chemical sensitivity shows diverse symptoms triggered by extremely small quantities of variable chemicals in indoor air.

It has been reported that *p*-dichlorobenzene causes adverse effects among exposed populations, particularly in those with occupational exposure.[8)] The Japan Society for Occupational Health recommends the Occupational Exposure Limits (OELs) as reference values for preventing adverse health effects on workers caused by occupational exposure to chemical substances, continuous or intermittent noise, *etc*., in which the OEL of *p*-dichlorobenzene is 10 ppm.[9)] On the other hand, nonoccupational GLV for an indoor concentration of *p*-dichlorobenzene in Japan is 0.04 ppm.[4)] The relationship between SBS symptoms and *p*-dichlorobenzene exposure or serum level of *p*-dichlorobenzene has not been reported. The widespread exposure of populations to *p*-dichlorobenzene requires more detailed investigation.

Case 2

Table 2 shows the summary results of serum VOC concentrations in patient B together with those of four other patients with other onsets such as moving into a new or newly remodeled house. The serum 2-ethyl-1-hexanol concentration of patient B was 4.6 ng/ml, the highest of the seven VOCs analyzed in this study, and was more than 7.7-fold higher than in the other four patients. Table 3 shows the summary results of sample analysis of patient B's breathing-zone air, and indoor air in an office and a seminar room mainly used by patient B together with her home, for seven of the 41 VOCs examined. 2-Ethyl-1-hexanol was detected in her breathing-zone air (18 $\mu g/m^3$), indoor air in her office (13 $\mu g/m^3$), and a seminar room (44 $\mu g/m^3$), while 2-ethyl-1-hexanol was not detected in indoor air in her home. These results suggest that her el-

Table 2. Serum VOC Concentrations of Patient B and Four Other Patients

VOCs	Concentration (ng/ml)				
	Patient B[a)]	Other patients			
		1	2	3	4
2-Ethyl-1-hexanol	4.6	0.6	<0.5	0.5	0.6
p-Dichlorobenzene	1.9	<0.5	<0.5	1.0	<0.5
Toluene	0.4	0.2	0.5	0.1	0.1
Benzene	0.1	<0.1	<0.1	<0.1	<0.1
Xylene	<0.1	<0.1	0.2	0.1	0.1
Ethylbenzene	<0.1	<0.1	0.1	<0.1	0.1
Styrene	<0.1	<0.1	0.1	<0.1	<0.1

a) Blood was drawn after the sampling of breathing-zone air and indoor air were finished.

Table 3. Selected VOC Concentrations of Patient B's Breathing-zone Air, and Indoor Air in an Office, a Seminar Room and Her Home

VOCs	Concentration (μg/m^3)			
	Breathing-zone air	Indoor air		
		Office	Seminor room	Home (living)
2-Ethyl-1-hexanol	18	13	44	<2.8
p-Dichlorobenzene	20	<2.8	3.8	110
Toluene	54	49	49	23
Benzene	6.7	5.1	5.4	6.6
Xylene	10	9.9	9.8	18
Ethylbenzene	9.5	9.2	9.6	9.0
Styrene	<2.8	<2.8	<2.8	<2.8

evated serum 2-ethyl-1-hexanol level was due to daily exposure in the university building.

The increase in 2-ethyl-1-hexanol in indoor air is a sign of dampness-related alkaline degradation of di-(2-ethylhexyl) phthalate used in building material for glue or in carpets with a polyvinyl chloride backing.[10)] The presence of 2-ethyl-1-hexanol is recognized in European countries and the U.S.A. as an indoor air pollutant.[7)] A possible relationship between SBS symptoms and indoor air 2-ethyl-1-hexanol has been reported, although the maximum indoor air concentration of 2-ethyl-1-hexanol was relatively low (20–30 μg/m^3).[11,12)] Additionally, *p*-dichlorobenzene was detected both in patient B's serum (1.9 ng/ml) and indoor air in her home (110 μg/m^3) but not in indoor air in the university building. It is assumed that *p*-dichlorobenzene is not responsible for her symptoms because she does not usually experience from respiratory symptoms while at home.

Measuring chemicals in blood is advantageous because we can calculate the body burden precisely. Blood levels of VOCs are known to be good predictors of VOC exposure, even though metabolism and excretion decrease levels over time.[13)] It should also be noted that the half-life of VOCs in blood is generally short, indicating that the data reflect only recent exposure.[14)] We found no relationship between serum VOC levels and SBS symptoms in the patients studied in our previous report.[6)] In the present study, we found two sensitive patients who had elevated serum levels of *p*-dichlorobenzene and 2-ethyl-2-hexanol; however, it is not an indoor environmental evaluation as such. At present, there is no universally accepted clinical definition of SBS and no adequate theory for its occurrence, although there are several theories.[15)] It is likely that SBS is multifactorial in origin, related to various factors and exposures.[1)] Further investigations are needed to evaluate the relationship between serum VOC levels and SBS symptoms.

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REFERENCES

1) Redlich, C. A., Sparer, J. and Cullen, M. R. (1997) Sick-building syndrome. *Lancet*, **349**, 1013–1016.
2) Hodgson, M. (2002) Indoor environmental exposures and symptoms. *Environ. Health Perspect.*, **110**, 663–667.
3) Torii, S. (2002) Sick house syndrome (in Japanese). *Nippon Rinsho*, **60** (Suppl 1), 621–627.
4) Ministry of Health, Labour and Welfare of Japan (2001) Committee on sick house syndrome: indoor air pollution progress report no. 3.
5) Saijo, Y., Kishi, R., Sata, F., Katakura, Y., Urashima, Y., Hatakeyama, A., Kobayashi, S., Jin, K., Kurahashi, N., Kondo, T., Gong, Y. Y. and Umemura, T. (2004) Symptoms in relation to chemicals and dampness in newly built dwellings. *Int. Arch. Occup. Environ. Health*, **77**, 461–470.
6) Kondo, F., Ikai, Y., Goto, T., Ito, Y., Oka, H., Nakazawa, H., Odajima, Y., Kamijima, M., Shibata, E., Torii, S. and Miyazaki, Y. (2006) Serum levels of volatile organic compounds in patients with sick building syndrome. *Bull. Environ. Contam. Toxicol.*, **77**, 331–337.
7) Kamijima, M., Sakai, K., Shibata, E., Yamada, T., Itohara, S., Ohno, H., Hayakawa, R., Sugiura, M., Yamaki, K. and Takeuchi, Y. (2002) 2-Ethyl-1-hexanol in indoor air as a possible cause of sick building symptoms. *J. Occup. Health*, **44**, 186–191.
8) Hill, R. H. Jr., Ashley, D. L., Head, S. L., Needham, L. L. and Pirkle, J. L. (1995) *p*-Dichlorobenzene exposure among 1000 adults in the United States. *Arch. Environ. Health*, **50**, 277–280.
9) Japan Society for Occupational Health (2004) Recommendation of occupational exposure limits. *J. Occup. Health*, **46**, 329–344.
10) Hodgson, A. T., Wooley, J. D. and Daisey, J. M. (1993) Emissions of volatile organic compounds from new carpets measured in a large-scale environmental chamber. *Air Waste*, **43**, 316–324.
11) Wieslander, G., Norbäck, D., Nordström, K., Walinder, R. and Venge, P. (1999) Nasal and ocular symptoms, tear film stability and biomarkers in nasal lavage, in relation to building-dampness and building design in hospitals. *Int. Arch. Occup. Environ. Health*, **72**, 451–461.
12) Norbäck, D., Wieslander, G., Nordström, K. and Wålinder, R. (2000) Asthma symptoms in relation to measured building dampness in upper concrete floor construction, and 2-ethyl-1-hexanol in indoor air. *Int. J. Tuberc. Lung Dis.*, **4**, 1016–1025.
13) Mannino, D., Schreiber, J., Aldous, K., Ashley, D., Moolenaar, R. and Almaguer, D. (1995) Human exposure to volatile organic compounds: a comparison of organic vapor monitoring badge levels with blood levels. *Int. Arch. Occup. Environ. Health*, **67**, 59–64.
14) Etzel, R. A. and Ashley, D. L. (1994) Volatile organic compounds in the blood of persons in Kuwait during the oil fires. *Int. Arch. Occup. Environ. Health*, **66**, 125–129.
15) Mandell, M. J. (1993) Non-specific symptoms in office workers: a review and summary of the literature. *Indoor Air*, **4**, 227–236.