Case Study

2-Ethyl-1-hexanol in Indoor Air as a Possible Cause of Sick Building Symptoms

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Key words: 2-Ethyl-1-hexanol, Volatile organic compounds (VOCs), Indoor air pollution, Sick building syndrome, Multiple chemical sensitivity, Sick house syndrome

Building-associated chemical hypersensitivity is one of the more topical issues in the occupational and environmental health field today. After years of debate, diverse symptoms of susceptible individuals triggered by extremely small quantities of variable chemicals in indoor air are now recognized as due to multiple chemical sensitivity (MCS)^{1,2}. Historically, there has been another disease entity caused by indoor air pollution. Its set of symptoms, typically headache and mucous membrane irritation, recognized among occupants of nonindustrial buildings such as offices and schools, has been defined as sick building syndrome (SBS)^{3,4}. The relatively higher prevalence of these symptoms among residents of the implicated buildings is a hallmark of SBS⁴.

Recently in Japan, indoor air pollution of newly constructed or renovated buildings has become an issue of health concern. Symptoms associated with formaldehyde or other volatile organic compounds (VOCs) emitted from the building are called 'sick house syndrome' (SHS). Though there is no established definition of SHS, it is considered to include both SBS and MCS. The disorder is acquired in relation to building construction or renovation as a documentable source of environmental exposure.

Here we report a patient with MCS suffering mainly

from respiratory symptoms due to low-level exposure to airborne chemicals, especially 2-ethyl-1-hexanol, in her office building. Some other building occupants also suffered symptoms related to the central nervous system, respiratory tract, and mucous membrane irritation. This study shows that 2-ethyl-1-hexanol, which is recognized in European countries and the United States as an indoor air pollutant emitted from commercial furniture or carpets with a polyvinyl chloride backing⁵⁻⁹, could elicit acute symptoms in susceptible individuals at a concentration range of $\mu\text{g}/\text{m}^3$.

Case report

A 61-yr-old female professor of foreign culture and literature visited us in December 2000, complaining of a non-productive cough, throat irritation, and sore eyes when she was in her university buildings (Buildings No. 1 and No. 2).

She began to suffer persistent cough and occasional slight fever in the fall of 1996, shortly after the construction of a new campus building (Building No. 3) started just outside her old office in Building No. 4 located in another satellite campus. Much dust and pungent solvents were emitted, and her symptoms appeared especially when she delivered lectures three times a week in Building No. 1 (constructed in March 1996 next to the planned site of Building No. 2 on the main campus). In March 1998, she moved to her new office in Building No. 2 just after its completion. Conscious of her building-related illness, she had her new office baked out before moving in and usually kept the ventilator running. The annoying symptoms subsided as long as she remained in her new office, but they recurred in many other parts of Buildings No. 1 and No. 2. One of the worst places was a faculty meeting room in Building No. 2 where administrative meetings took place every other week. These symptoms became subjectively severer after fall 1999, when a male professor on the patient's floor started to use ethyl ether and acetone occasionally in his laboratory for the extraction of food ingredients. The strong odor from these solvents could be smelled in the corridor just outside her office whenever experiments were conducted. The air conditioning system on that floor was designed to take the indoor air from the male professor's laboratory and exhaust it in the corridor just outside her office. As a consequence, she had become more sensitive to the airborne chemicals shown in Table 1, suffering sore throat and coughs anywhere almost immediately and incessantly when she was exposed to them, so that she always wore an activated carbon mask to lower her exposure.

Her main symptoms in the faculty meeting room were throat irritation, cough, and sore eyes, along with headache, heavyheadness, and blurred vision. She also had a slight fever in the evening after spending several

Received Dec 15, 2001; Accepted March 13, 2002

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Table 1. VOC-emitting places and products which elicited the patient's symptoms

Faculty meeting room and other locations in Building No. 2 (2-ethyl-1-hexanol and other VOCs)
Building No. 1
Whiteboard pen* (ethyl acetate, methyl isobutyl ketone)
Solvents (ethyl ether, ethyl alcohol, acetone, and others)
New journals and flyers printed on poor-quality paper
Wax
Dry-cleaned cloths
Nail polish remover
A specific perfume
Hair-care products
Bathroom deodorant

Identified chemicals are shown in parentheses. *Patch tests showed the ink of the pen and ethyl acetate induced delayed reactions, but methyl isobutyl ketone did not.

hours there. We measured airborne VOC concentrations in Building No. 2 in March and August 2001, when the same symptoms persisted. The results showed that 2-ethyl-1-hexanol was a predominant VOC in indoor air (see next section).

Since her symptoms resembled occupational asthma, peak expiratory flow rates (PEFR) were measured three times a day (morning, afternoon and evening) between January and June 2001. Although there was a decreasing PEFR tendency in the afternoons and subsequent evenings of workdays when faculty meetings were held (from which she recovered on her days off), the extent of variance was about 6% at most, which was not considered significant. Second, provocative spirometry was conducted before, during and after patch tests on 2-ethyl-1-hexanol and phthalates. This provocation test was planned after careful consideration to reduce the risk of asthmatic attack which might have occurred as a consequence of inhalation challenge test. Forced expiratory volume in one second ($FEV_{1.0}$) and $FEV_{1.0}\%$ were unchanged, though her throat irritation occurred during the test. No further bronchial provocation test was undertaken because she suffered a slight fever, an abnormal feeling of inflamed oral cavity and could not eat well for 2 d after the spirometry. The patch-tested chemicals were 2-ethyl-1-hexanol, phthalates, and other common VOCs along with standard chemicals designated by the Japanese Society for Contact Dermatitis¹⁰⁾. The results showed that, among the tested VOCs, ethyl ether, acetaldehyde and benzaldehyde induced immediate reactions and that ethyl ether, ethyl acetate, ethyl alcohol, acetaldehyde, and various kinds of oil for cosmetics, soaps, perfumes and drugs induced delayed reactions (Sugiura *et al.*, manuscript in preparation). Her clinical

manifestations met the definition of MCS proposed by Cullen and other researchers^{1,2)}. She had no history of atopy or respiratory diseases, was a nonsmoker and nondrinker because of the itching sensation and urticaria she experienced after drinking, both of which she first recognized at the age of 24. Another distinct memory was that her skin flared up when a disinfectant ethyl alcohol was applied before an operation at the age of 41. Her father also did not drink.

Measurements of airborne chemical concentrations in Building No. 2

Airborne concentrations of chemicals were measured in the faculty meeting room and the patient's office in Building No. 2 at the end of March 2001. The following measurement was conducted in August 2001 in the above two rooms and additional areas in the same building. Building No. 1 measurements were scheduled for later because it belonged to a different department. VOCs were actively sampled in charcoal tubes (gas tube for organic solvents, Sibata Scientific Technology, Japan) at a height of 1.2–1.5 m above the floor, with an air sampling rate of 1.0 l/min for 24 h. The collected gas was extracted with CS_2 and determined by means of a gas chromatograph with a mass spectrometer (GC-MS). The GC-MS (5890 Series II/5971A, Hewlett Packard, USA) was equipped with a 60 m $\times$ 0.25 mm i.d. capillary column coated with a 1.0 μ m film of DB-1 (Agilent Technologies, USA). The GC oven temperature was first maintained at 45°C for 5 min, then programmed to 300°C at 10°C/min and held at 300°C for 4 min. The analysis was performed with a helium flow rate of 0.9 ml/min under a scan monitoring mode first to cover all the major peaks, followed by a selected-ion monitoring mode targeting 42 chemicals routinely measured in Japan¹¹⁾. Carbonyl compounds were collected with diffusive samplers packed with silica gel containing 2,4-dinitrophenylhydrazine (Aldehyde diffusive sampling device, Sigma-Aldrich, Japan). The samplers were left in the rooms for 24 h. Gas collected was extracted with acetonitrile and identified by means of a high-performance liquid chromatograph (LC-9A, Shimadzu, Japan) with UV detection at 360 nm. The analytical column was a Discovery RP-Amide C16 (25 mm $\times$ 4.6 mm, Sigma-Aldrich, USA). The results showed that 2-ethyl-1-hexanol was the predominant indoor air pollutant in Building No. 2 (Tables 2 and 3). In March, the difference between the office and the meeting room in 2-ethyl-1-hexanol concentration was about 380 μ g/m³, whereas the differences in other pollutants were less than 10 μ g/m³ (Tables 2-1 and 2-2).

Questionnaire survey of faculty/staff members and PEFR measured by a male professor

A questionnaire survey was conducted on 54 faculty

Table 2-1. Airborne concentrations (mg/m³) of volatile organic compounds in March measured by active technique

	Faculty meeting room (a)	Office (b)	a-b
2-Ethyl-1-hexanol	469.0	85.3	383.7
Toluene	30.6	20.7	9.9
Ethyl acetate	15.5	7.6	7.9
<i>m, p</i> -Xylene	7.1	4.9	2.2
Ethyl benzene	6.4	4.4	2.0
Methyl ethyl ketone	4.4	2.0	2.4
2, 2, 4-Trimethylpentane	3.6	1.4	2.2
<i>n</i> -Decane	3.2	1.9	1.3
Benzene	2.9	1.6	1.3
<i>n</i> -Hexane	2.8	1.9	1.0
1, 2, 4-Trimethylbenzene	2.7	1.5	1.2
<i>o</i> -Xylene	2.5	1.9	0.6
Trichloroethylene	2.4	1.4	1.0
Butyl alcohol	2.2	3.7	-1.5
Methyl isobutyl ketone	1.8	0.7	1.0
<i>n</i> -Nonane	1.7	1.0	0.7
<i>n</i> -Undecane	1.7	1.0	0.7
<i>n</i> -Dodecane	1.5	1.3	0.2
Tetrachloroethylene	1.3	1.1	0.2
<i>n</i> -Heptane	1.2	0.9	0.4
<i>n</i> -Tetradecane	1.1	1.4	-0.3
α -Pinene	1.1	1.3	-0.2
<i>p</i> -Dichlorobenzene	1.1	0.8	0.3
<i>n</i> -Tridecane	1.1	1.3	-0.2
Nonyl aldehyde	0.9	1.7	-0.8
1, 3, 5-Trimethylbenzene	0.8	0.5	0.3
<i>n</i> -Octane	0.6	0.4	0.2
Carbon tetrachloride	0.6	0.3	0.3
Butyl acetate	0.6	0.2	0.4
Chloroform	0.4	0.6	-0.2
Styrene	0.4	0.4	0.0
<i>n</i> -Hexadecane	0.4	1.0	-0.6
<i>n</i> -Pentadecane	0.3	0.8	-0.5
Limonene	0.3	1.0	-0.7
1, 2, 3-Trimethylbenzene	0.3	0.9	-0.6
1, 1, 1-Trichloroethane	0.2	0.1	0.1
1, 2, 4, 5-Tetramethylbenzene	0.2	0.1	0.1
1, 2-Dichloropropane	0.1	1.7	-1.6
2, 4-Dimethylpentane	BDL	BDL	-
Chlorodibromomethane	BDL	BDL	-
1, 2-Dichloroethane	BDL	BDL	-
Decyl aldehyde	BDL	BDL	-

BDL, below detection limit. Average temperature and relative humidity indoors were 22.5°C and 38%, respectively.

and staff members in Building No. 2. They were asked whether they had experienced subjective symptoms in areas including 1) the faculty meeting room, 2) their offices, 3) classrooms, 4) seminar rooms, 5) corridors, in Building No. 2, and 6) classrooms and seminar rooms in

Building No. 1. Thirty-one subjects (20 males and 11 females, aged 48.5 ± 9.5 (average $\pm$ S.D.)) responded. Among them, 13 (8 males and 5 females) complained of the area-associated symptoms (Table 3). PEFR was measured in a 59-yr-old male professor three times every

Table 2-2. Airborne concentrations ($\mu\text{g}/\text{m}^3$) of carbonyl compounds in March measured by passive technique

	Faculty meeting room (a)	Office (b)	a-b
Formaldehyde	19.0	9.7	9.2
Acetone	12.9	18.4	-5.5
Acetoaldehyde	3.4	4.5	-1.1
<i>p</i> -Tolualdehyde	1.0	BDL	-
Propionaldehyde	0.8	1.0	-0.3
Butyraldehyde	0.7	1.0	-0.4
Hexaldehyde	BDL	BDL	-
<i>o, m</i> -Tolualdehyde	BDL	BDL	-
Acrolein	BDL	BDL	-
Crotonaldehyde	BDL	BDL	-
Benzaldehyde	BDL	BDL	-
Isovaleraldehyde	BDL	BDL	-
Valeraldehyde	BDL	BDL	-
2, 5-dimethylbenzaldehyde	BDL	BDL	-

BDL, below detection limit.

Table 3. Building-related subjective symptoms in faculty/staff members and airborne concentrations of major VOCs by areas in August ($\mu\text{g}/\text{m}^3$)

	Building No. 2					Building No. 1	
	Faculty meeting room (8:31)	Office ^b (2:31)	Classroom ^b (1:29)	Seminar room ^b (5:27)	Corridor ^b (2:31)	Outside of Building No. 2 (0:31)	Classroom and seminar room (6:27)
("Yes" replies: Eligible respondents ^a)							
Headache	2				1		1
Dizziness	1						
Nausea	3						
Sore eyes	4	1		1	2		4
Blurring of vision	2		1	1	1		
Itching eyes				1			
Nasal irritation	3		1	1	1		2
Sneezing, running nose	1		1	1	1		1
Smell paint or adhesives	4			3			3
Frequent cough	3	1	1	3			2
Difficult breezing, nasal/throat congestion	2			1			1
Sore throat	2		1	1	1		2
2-Ethyl-1-hexanol	408	222	198	1086	164	0.9	-
Toluene	16.7	13.5	15.6	17.0	14.7	10.5	-
Butyl alcohol	5.5	21.0	6.6	38.4	14.5	0.7	-
Formaldehyde	81.7	43.9	70.8	82.8	43.8	6.6	-
Acetone	18.1	18.2	14.1	32.5	34.8	4.6	-
Acetoaldehyde	10.4	13.9	4.7	13.3	10.9	1.4	-

^a Those who answered 'Don't go there' were considered ineligible. ^b VOC concentrations were measured at the end of August (average temperature and relative humidity indoors and outdoors were 24.5°C and 78%, 27.5°C and 73%, respectively) under the worst condition at each site. Not every respondent went into the measured sites under the same conditions. Underlined figures include the present MCS patient. VOCs detected at more than 10 $\mu\text{g}/\text{m}^3$ were shown in this table. -, not measured.

day (morning, afternoon and evening) for 10 d. He had been coughing in his office, the faculty meeting room, a seminar room in Building No. 2, and a room in Building No. 1. No change in PEFR was detected throughout workdays and days off.

Discussion

The present study revealed that 2-ethyl-1-hexanol, an skin and eye irritant^{12, 13}, was a predominant VOC inside Building No. 2. Its concentration was about 400 $\mu\text{g}/\text{m}^3$ in the faculty meeting room, or 2–5 times higher than in the patient's office. In March, the differences between the two rooms in identified VOC concentrations was less than 10 $\mu\text{g}/\text{m}^3$ except for 2-ethyl-1-hexanol, suggesting that it could be a causative chemical involved in sick building symptoms in susceptible individuals.

Norbäck and colleagues recently showed a possible relationship between various symptoms and airborne 2-ethyl-1-hexanol^{14–16}. The maximum concentration of 2-ethyl-1-hexanol in their studies was 20–30 $\mu\text{g}/\text{m}^3$. Although these concentrations were much lower than those in the present study, 66% of the subjects studied had at least one ocular symptom (e.g., sore or itchy eyes)¹⁶, and a positive association between asthma symptoms and 2-ethyl-1-hexanol was suggested¹⁴.

The mechanism of respiratory symptoms in the present MCS case is unclear. Although her symptoms resembled cough variant asthma, PEFR or provocative spirometry failed to show an asthmatic pattern. A skin patch test for 2-ethyl-1-hexanol also did not reveal any immediate or delayed reaction. These results suggest that the throat irritation and cough resulted from the irritating nature of 2-ethyl-1-hexanol. As for ethyl ether, ethyl acetate and benzaldehyde (a toluene metabolite), however, our attention was drawn to the possible links between the positive reactions in the patch tests, her symptoms, and the corresponding episodes in which the patient was heavily exposed to the chemicals. It would be reasonable to attribute her sensitization to ethyl acetate and benzaldehyde to the construction of Building No. 3 in 1996, and ethyl ether to her colleague's experiment beginning in the fall of 1999. In contrast, she had been sensitized to ethyl alcohol and/or acetaldehyde already in her twenties, long before the onset of building-associated MCS, namely SHS. Whether nondrinkers are at higher risk for MCS or SHS remains an interesting problem for future research.

Our last discussion concerns the source of 2-ethyl-1-hexanol. It is noteworthy that the 3-yr-old building still emitted the chemical at noticeably higher concentrations than other VOCs whose levels generally decreased significantly within a year after building completion^{17, 18}. 2-Ethyl-1-hexanol is a dampness-related emission resulting from the alkaline degradation of the plasticizer di-(2-ethylhexyl) phthalate used in building materials for

glue or in carpets with a polyvinyl chloride backing^{5, 6, 8}. Follin detected 2-ethyl-1-hexanol in concrete slabs at its highest concentrations beneath a surface covered with vinyl carpet⁹. In the present case, interior materials such as floor tiles, ceiling board and wall cloth appeared to be different in various areas in Building No. 2, but they must share some common building material(s), since 2-ethyl-1-hexanol was the leading pollutant in this building. Finally, it also remains to be clarified how much di-(2-ethylhexyl) phthalate the indoor air contained because the present analysis method could not identify phthalate ester. These remaining questions are at present under investigation. In conclusion, more attention needs to be paid to 2-ethyl-1-hexanol as a possibly causative chemical in sick building symptoms, and its emission controls should be established.

References

- 1) Cullen MR. Low-level environmental exposures. In: Rosenstock L, Cullen MR, eds. Textbook of clinical occupational and environmental medicine. 2nd ed. Philadelphia: W.B. Saunders Company, 1994: 667–672.
- 2) Harrison RJ. Multiple chemical sensitivity. In: LaDou J, ed. Occupational and environmental medicine. Stamford: Appleton and Lange, 1997: 752–758.
- 3) Fischman ML. Building-associated illnesses. In: LaDou J, ed. Occupational and environmental medicine. 2nd ed. Stamford: Appleton and Lange, 1997: 723–732.
- 4) Kreiss K. Sick building syndrome and building-related illness. In: Rom WN, ed. Environmental and occupational medicine. 3rd ed. Philadelphia: Lippincott-Raven Publishers, 1998: 1471–1477.
- 5) Follin T. Measurements during airing out pollutions from concrete slabs. In: Proceedings of the 7th International Conference on Indoor Air Quality and Climate. Vol. 3. Tokyo: Organizing Committee of the 7th International Conference on Indoor Air Quality and Climate, 1996: 65–70.
- 6) Pleil JD, Whiton RS. Determination of organic emissions from new carpeting. Appl Occup Environ Hyg 1990; 5: 693–699.
- 7) U.S. Environmental Protection Agency. Environmental technology protocol verification report. Emissions of VOCs and aldehydes from commercial furniture. Research Triangle Park: Research Triangle Institute, 1999.
- 8) Hodgson AT, Wooley JD, Daisey JM. Emissions of volatile organic compounds from new carpets measured in a large-scale environmental chamber. J Air Waste Manage Assoc 1993; 43: 316–324.
- 9) European Collaborative Action 'Indoor air quality and its impact on man'. Total volatile organic compounds (TVOC) in indoor air quality investigations (Report No. 19, EUR 17675 EN). Luxembourg: Office for Official Publications of the European Community, 1997.
- 10) Natsuaki M. Results of patch testing with standard allergens of the Japanese Society for Contact Dermatitis

- and topical nonsteroidal anti-inflammatory preparations in 1998. *Environ Dermatol* 2000; 7: 1–5.
- 11) Ministry of Health and Welfare, Japan. Report on indoor air pollution by volatile organic compounds in dwellings in Japan. 1999 (in Japanese).
  - 12) Smyth HF, Carpenter CP, Weil CS, Pozzani UC, Striegel JA, Nycum JS. Range-finding toxicity data: List VII. *Am Ind Hyg Assoc J* 1969; 30: 470–476.
  - 13) Scala RA, Burtis EG. Acute toxicity of a homologous series of branched-chain primary alcohols. *Am Ind Hyg Assoc J* 1973; 34: 493–499.
  - 14) Norbäck D, Wieslander G, Nordström K, Wålinder R. 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* 2000; 4: 1016–1025.
  - 15) Wålinder R, Wieslander G, Norbäck D, Wessen B, Venge P. Nasal lavage biomarkers: effects of water damage and microbial growth in an office building. *Arch Environ Health* 2001; 56: 30–36.
  - 16) Wieslander G, Norbäck D, Nordström K, Wålinder R, Venge P. 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* 1999; 72: 451–461.
  - 17) Arashidani K, Hori H, Yoshikawa M, Ishimatsu S, Kawamoto T, Kodama Y. Measurement of volatile organic compounds, HCHO and NO₂ concentrations in a new building. In: *Proceedings of the 8th International Conference on Indoor Air Quality and Climate*. Vol. 2. London: Construction Research Communications Ltd, 1999: 483–488.
  - 18) Yu CWF, Crump DR, Squire RW. The impact of VOC emission on the indoor air quality of a newly built energy efficient office building at BRE. In: *Proceedings of the 8th International Conference on Indoor Air Quality and Climate*. Vol. 2. London: Construction Research Communications Ltd, 1999: 489–494.