Statistical power calculations were performed using Epistat (Finnish Institute of Occupational Health). This study sample size had at least 80% power (two-sided test significant, α of 0.05) to detect an OR of at least 2.5, following the calculations used in previous studies [18–20]. We used the dominant model for *GSTM1* and *GSTT1* and the recessive model for *ALDH2* and *PON1* in the test analysis.

Ethical considerations

The Ethics Review Board of Miyazaki University (no. 82, April 9, 2003) and Kumamoto University (no. 168, May 11, 2011) approved this study, following the ethical guidelines for human genome research. All participants were given full explanations of informed consent and the full protection of their personal data in written form.

Results

Table 1 presents the frequency of MCS, sick house syndrome, and allergic diseases such as asthma, allergic coryza, and atopic dermatitis. Four subjects reported history of diagnosis of MCS, three of whom also had history of allergy. The QEESI score and genotypes of these 4 subjects were as follows: (1) Q1 (27), Q2 (15), Q3 (36), *GSTM1 null*, *GSTT1 null*, *ALDH2*1/*1* and *PON1 Arg/Arg*; (2) Q1 (38), Q2 (5), Q3 (14), *GSTM1 null*, *GSTT1 null*, *ALDH2*1/*1* and *PON1 Arg/Arg*; (3) Q1 (27), Q2 (30), Q3 (78), *GSTM1 non-null*, *GSTT1 non-null*, *ALDH2*1/*1* and *PON1 Arg/Arg*; and (4) Q1 (9), Q2 (12), Q3 (23), *GSTM1 non-null*, *GSTT1 null*, *ALDH2*1/*2* and *PON1 Arg/Arg*. No subjects in this study population had diagnosis of sick house syndrome.

Chemical sensitivity was estimated by high cutoff values in the three subscales of chemical sensitivity ($\geq$40), other chemical sensitivity ($\geq$25), and symptom severity ($\geq$40). The percentage of subjects to whom high cutoff values were applied for the subscales of chemical sensitivity, other chemical sensitivity, and symptom severity were 7.1%, 3.1%, and 6.8%, respectively. The risks for chemical sensitivity as defined by Miller and Prihoda, estimated by high cutoff values on two subscales or three subscales, were 2.9% ($n = 31$) and 0.7% ($n = 8$), respectively.

When Hojo et al. [17] confirmed that the QEESI is effective for screening Japanese MCS patients, they suggested that the cutoff values for Japanese subjects should be chemical sensitivity score $\geq$40 and symptom severity score $\geq$20. In our study population, 4.3% ($n = 47$) of the subjects met that criteria and were defined as the cases (Table 2). There was a significant difference between the cases and controls in smoking status. However, no significant differences between the two groups in drinking status were observed.

Next we examined the association between genetic variants in *GSTM1*, *GSTT1*, *ALDH2*, and *PON1* and chemical sensitivity in the total population and the case–control population. The frequencies of genotypes for all examined gene variants by chemical sensitivity subscale score are presented in Table 3. On the chemical sensitivity subscale, 32.7% scored 0, 42.7% scored from 1 to 19, 17.5% scored from 20 to 39, and 7.1% scored 40 or higher. On the other chemical sensitivity subscale, 26.6% scored 0, 67.9% scored from 1 to 19, 5.0% scored from 20 to 39, and 0.5% scored 40 or higher (Electronic Supplementary Table S1). On the symptom severity subscale, 15.5% scored 0, 54.9% scored from 1 to 19, 22.8% scored from 20 to 39, and 6.8% scored 40 or higher (Electronic Supplementary Table S2). No significant difference in frequency was found for any gene variant between any levels in the total population or on any subscale of the QEESI. Similarly, there were no significant differences between the QEESI scores of genetic variants in *GSTM1*, *GSTT1*, *ALDH2*, and *PON1* (Table 3, Electronic Supplementary Tables S1 and S2).

The genotype data were also analyzed in the case–control design using logistic regression analyses with chemical sensitive status (cases: chemical sensitivity score $\geq$40 and symptom severity score $\geq$20) as outcome variables and genotype as the predictor variable, as presented in Table 4. No categorical predictor variable reached statistical significance. To check the effect of the genes in combination with smoking status, we calculated the OR for data classified by smoking status and by gene genotypes. The summarized data and ORs are presented in Table 5 together with 95% CIs. None of the distributions of genotypes showed any significant differences from the controls.

Discussion

This study focused on gene polymorphisms as a factor of chemical sensitivity, and analyzed *GSTM1*, *GSTT1*, *ALDH2*, and *PON1*.

Schnakenberg et al. [21] observed that the *GSTM1* and *GSTT1* gene deletion genotype occurred significantly more often in those individuals in German populations who reported chemical-related hypersensitivity. On the other hand, the allele and genotype frequencies of *GSTM1* and *GSTT1* were similar in Italian MCS patients and control populations [22]. In our study, no significant differences between the genotype frequency of *GSTT1* and *GSTM1* were found for any severity of three QEESI subscales or in the case–control study. The contradictory results are

Table 3 Association of QEESI chemical sensitivity subscale score with variants of *GSTM1*, *GSTT1*, *ALDH2*, and *PON1*

Gene	Genotype	QEESI score					
		0 *n* (%) 354 (32.7)	1–19 *n* (%) 463 (42.7)	20–39 *n* (%) 190 (17.5)	40–100 *n* (%) 77 (7.1)	Total *n* (%) 1,084 (100)	*P* value[a]
GSTM1	*Non-null*	152 (42.9)	213 (46.0)	95 (50.0)	36 (46.8)	496 (45.8)	
	Homozygous-null	202 (57.1)	250 (54.0)	95 (50.0)	41 (53.2)	588 (54.2)	0.47
GSTT1	*Non-null*	199 (56.2)	257 (55.5)	99 (52.1)	48 (62.3)	603 (55.6)	
	Homozygous-null	155 (43.8)	206 (44.5)	91 (47.9)	29 (37.7)	481 (44.4)	0.49
ALDH2	**1/*1*	222 (62.7)	276 (59.6)	113 (59.5)	54 (70.1)	665 (61.3)	
	**1/*2*	109 (30.8)	166 (35.9)	66 (34.7)	20 (26.0)	361 (33.3)	
	**2/*2*	23 (6.5)	21(4.5)	11 (5.8)	3 (3.9)	58 (5.4)	
	**1/*2* or **2/*2*	131 (37.3)	187 (40.4)	77 (40.5)	23 (29.9)	419 (38.7)	0.30[b]
PON1	*Arg/Arg*	147 (41.5)	178 (38.5)	81 (42.6)	33 (42.8)	439 (40.5)	
	Arg/Gln	185 (52.3)	253 (54.6)	91(47.9)	38 (49.4)	567 (52.3)	
	Gln/Gln	22 (6.2)	32 (6.9)	18 (9.5)	6 (7.8)	78 (7.2)	
	Arg/Gln or *Gln/Gln*	207 (58.5)	285 (61.5)	109 (57.4)	44 (57.2)	645 (59.5)	0.68[c]

[a] *P* value, chi-square test. $P < 0.05$, difference significant

[b] **1/*2* or **2/*2* against **1/*1*

[c] *Arg/Gln* or *Gln/Gln* against *Arg/Arg*

Table 4 Association of cases and controls defined by QEESI score with the variants of *GSTM1*, *GSTT1*, *ALDH2*, and *PON1*

Gene	Genotype	Cases (CSP) $n = 47$ (%)	Controls $n = 1037$ (%)	Crude OR[a]	*P* value[b]	Adjusted OR[b,c]
GSTM1	*Non-null*	20 (42.6)	476 (45.9)	1		1
	Homozygous-null	27 (57.4)	561 (54.1)	1.15 (0.61–2.15)	0.62	1.16 (0.64–2.10)
GSTT1	*Non-null*	31 (66.0)	572 (55.2)	1		1
	Homozygous-null	16 (34.0)	465 (44.8)	0.63 (0.33–1.22)	0.12	0.61 (0.33–1.13)
ALDH2	**1/*1*	32 (68.1)	633 (61.0)	1		1
	**1/*2*	13 (27.7)	348 (33.6)			
	**2/*2*	2 (4.2)	56 (5.4)			
	**1/*2* or **2/*2*	15 (31.9)	404 (39.0)	0.73 (0.37–1.42)	0.18[d]	0.63 (0.32–1.24)[d]
PON1	*Arg/Arg*	19 (40.4)	420 (40.5)	1		1
	Arg/Gln	25 (53.2)	542 (52.3)			
	Gln/Gln	3 (6.4)	75 (7.2)			
	Arg/Gln or *Gln/Gln*	28 (59.6)	617 (59.5)	1.00 (0.53–1.88)	0.85[e]	1.06 (0.58–1.94)[e]

[a] Odds ratio (OR) and 95% confidence interval (95% CI)

[b] *P* value, chi-square test. $P < 0.05$, difference significant

[c] ORs were adjusted for age (continuous), gender, smoking, and drinking

[d] **1/*2* or **2/*2* against **1/*1*

[e] *Arg/Gln* or *Gln/Gln* against *Arg/Arg*

mainly due to the inclusion criteria adopted by the different studies.

Our study is the first to analyze the association between *ALDH2* variants and chemical sensitivity, and no significant association was observed in our Japanese population. This result suggests that the *ALDH2* variants may not be involved in CSP.

PON1 plays a major role in biodegradation of various organophosphates that can function as potent cholinesterase inhibitors. Previous studies suggested that the polymorphic site in *PON1* was related to an increased risk of MCS [23] and Gulf War Syndrome, which is an MCS-related syndrome [15]. However, no significant association between the Gln192Arg polymorphism and *PON1* was

Table 5 Odds ratio for genotypes related to CSP by smoking status

Gene	Genotype	Nonsmokers, OR (95% CI)[a] $n = 481$ (44.6%)	Smokers (>once/week), OR (95% CI)[a] $n = 603$ (55.6%)
GSTM1	*Homozygous-null* versus *non-null* genotype	1.49 (0.69–3.23)	0.78 (0.30–2.01)
GSTT1	*Homozygous-null* versus *non-null* genotype	1.18 (0.36–3.92)	0.85 (0.32–2.23)
ALDH2	**1/*2* or **2/*2* versus **1/*1*	1.21 (0.37–4.00)	0.50 (0.15–1.67)
PON1	*Arg/Gln* or *Gln/Gln* versus *Arg/Arg*	1.24 (0.38–4.09)	1.08 (0.41–2.85)

[a] ORs were adjusted for age (continuous), gender, and drinking

obtained in our study. This trend in the MCS case–control design was reversed in the general population samples, perhaps reflecting that the *PON1* polymorphism played a minor or no role in the development of MCS in our population. In support of our study, Wiesmuller et al. [24] failed to detect an association between *PON1* polymorphism and self-reported MCS in a population sample.

On the other hand, we tried to define chemical sensitivity cases by Miller and Prihoda and estimated the risk for the genetic variants of *GSTM1*, *GSTT1*, *ALDH2*, and *PON1*, respectively. However, no case–control differences were observed in each genotype of the 4 genes.

Smoking status was significantly lower in the cases than in the controls. Several reports suggest that MCS patients who are aware of their chemical intolerance avoid exogenous chemicals such as those from smoking [23, 24]. Tobacco smoke contains many kinds of chemicals, including formaldehyde and acetaldehyde [25]. For these reasons, we hypothesize that the genotypes of *GSTM1*, *GSTT1*, *ALDH2*, and *PON1* might contribute to development of CSP in smokers. However, among the smokers there were no significant differences between CSP and controls in the *GSTM1*, *GSTT1*, *ALDH2*, and *PON1* genotypes.

In the present study, no significant differences between sequence variations of *GSTM1*, *GSTT1*, *ALDH2*, and *PON1* were found between the CSPs and controls. One possible weakness of our study design is a lack of assessments of environmental exposure to chemicals metabolized by the examined enzymes. It is plausible that gene–environment interactions exist, and the genetic variations of metabolic enzymes may either confer protection against or increase risk from harmful effects of chemical exposure. A second problem is the possibility that the subject sample we defined, following the QEESI protocols, was not a correct sampling of MCS. Our survey included the other chemical sensitivity subscale, but not life impact. Extrapolating from the results of Hojo et al., our defined cases whose scores exceeded the two cutoff values of chemical sensitivity ≥ 40 and symptom severity ≥ 20 were considered to be equivalent to 65% of the patients suspected to have MCS and 7% of the healthy controls. This screening criteria means that detecting the condition has sensitivity of 65% and specificity of 93%. It is unlikely that sensitivity, specificity, positive predictive value, and negative predictive value are influenced by the prevalence of the disease. As a result of that, we might not have been able to find the effect of important genotypes. A future strategy could be to subgroup patients according to symptoms, which may be genetically more homogeneous that a patient population as whole.

In conclusion, an association between risks for CSP-related MCS and genetic variation in biologically plausible candidate genes was not observed. Additionally, our results suggest that an exact case criterion is required to determine the actual importance to MCS of genetic variants in genes that encode metabolic enzymes.

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Conflict of interest No conflicts of interest.

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Chapter 15
Investigation of Air Pollution in Large Public Buildings in Japan and of Employees' Personal Exposure Levels

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15.1 Introduction

Approximately 80% of our lives are spent in indoor air environments such as homes or work places. The indoor air quality is often worse than that of the outdoor air, also it contains many pollutants. Jarke et al. (1981) identified 118 chemicals in the air inside new buildings and found that indoor pollutants probably arise from many components, such as the carpeting, clothing, and furniture. Many studies on indoor air pollution (Jia et al. 2008; Osawa and Hayashi 2009; Park and Ikeda 2006; Taneja et al. 2008) and its influence on health (Azuma et al. 2007; Ciencewicki and Jaspers 2007; Gomzi et al. 2007; Osman et al. 2007; Takigawa et al. 2010; Zuraimi et al. 2007) have been conducted.

In Japan, a major problematic change in indoor air environment has been recently recognized. This new problem is caused by highly air-tight houses incorporating adiabatic and other new building materials, and can lead to health problems. Residents in newly built homes complained of discomfort and illness related to this problem in the 1990s. These symptoms, called the sick house syndrome, have been studied in Japan. The symptoms are irregular and can not be distinguished from the sick building syndrome (SBS); socially, they have become a significant problem. The Ministry of Health, Labor, and Welfare (MHLW) of Japan, in cooperation with the Ministry of Land, Infrastructure, Transport, and Tourism (MLIT), Ministry of Economy, Trade, and Industry (METI), and Ministry of Agriculture, Forestry, and Fisheries (MAFF), have helped in controlling these sick house problems understanding the source and characteristics of indoor air pollution, indicating a concentration index (guideline) as a control policy, and developing methods for diagnosis and treatment. In addition, at the same time, the MLIT investigated pollution mechanisms and methods of calculating concentrations on the basis of the mechanisms, suggested designs

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Table 15.1 Japanese guidelines for acceptable levels of individual VOCs and aldehydes

Compound	Guideline value	Year of enforcement
Formaldehyde	100 μg/m^3 (80 ppb)	June, 1997
Toluene	260 μg/m^3 (70 ppb)	June, 2000
Xylene	870 μg/m^3 (200 ppb)	June, 2000
p-Dichlorobenzene	240 μg/m^3 (40 ppb)	June, 2000
Ethylbenzene	3,800 μg/m^3 (880 ppb)	Dec, 2000
Styrene	220 μg/m^3 (50 ppb)	Dec, 2000
Chlorpyrifos	1 μg/m^3 (0.07 ppb)	Dec, 2000
For children:	0.1 μg/m^3 (0.007 ppb)	
Di-n-butyl phthalate	220 μg/m^3 (20 ppb)	Dec, 2000
Tetradecan	330 μg/m^3 (40 ppb)	July, 2001
Di-(2-ethylhexyl) phthalate	120 μg/m^3 (7.6 ppb)	July, 2001
Diazinone	0.29 μg/m^3 (0.02 ppb)	July, 2001
Acetaldehyde	48 μg/m^3 (30 ppb) (300 μg/m^3 (180 ppb), WHO)	Jan, 2002
Fenobucarb	33 μg/m^3 (3.8 ppb)	Jan, 2002
Total VOC	400 μg/m^3, advisable value	Dec, 2000

to meet the guidelines, while the developed ventilation control technology, and the METI and MAFF developed low-emissive materials and effective ventilation equipment and legislated standards, greatly contributing to the amendment of the Building Standards Law (BSL). The MHLW established the guideline level for formaldehyde (100 μg/m^3) in 1997 and then for 12 other chemicals, as shown in Table 15.1. Afterward, indoor air quality at individual houses improved rapidly, as shown in the discussion below.

On the other hand, air pollution in large buildings open to the public, such as museums, university buildings, department stores, and amusement facilities are not examined properly. However, it is necessary to investigate the indoor air quality of those buildings because many people visit them for the purpose of education, shopping, and entertainment. This study examined the air environment of various large buildings in Japan and the chemical exposure of employees in these buildings. Consequentially, the Act on Maintenance of Sanitation in Buildings, enforced by the MHLW, prevented the spread of SBS, which surfaced in developed countries due to policies to save energy by reducing the ventilation rate.

15.2 Methods

15.2.1 Buildings Studied

We investigated indoor and outdoor air quality at schools, book stores, hotels, a department store, a city hall, shopping malls, hotels, theaters, museums, and amusement facilities, including a pachinko parlor and a bowling alley in Japan. Brief information on these buildings is provided in Table 15.2. The survey was performed in 2004–2006. Some countermeasures were performed in Japan before SBS became a concern in developed countries. Administrators of buildings with 3,000 m^2 or more of architectural floor space have been obligated to observe ventilation standards by the Act on Maintenance of Sanitation in Buildings. Amusement place B (a pachinko parlor), a beauty academy, and bookstore C in Table 15.2 are outside the scope of this law because their floor space is less than 3,000 m^2.

Table 15.2 Brief information on the buildings studied

Buildings	Purpose	Location	Year built	Floor area (m^2)
Amusement place A	Bowring alley	Kitakyushu	NA	NA
Amusement place B	Pachinko parlor	Miyazaki	NA	450
Beauty academy	School	Tokyo	2000	2,122
Bookstore A	Bookstore	Kitakyushu	1995	4,046
Bookstore B	Bookstore	Kitakyushu	1966	3,900
Bookstore C	Bookstore	Kitakyushu	NA	160
City hall	City hall	Kitakyushu	1959	4,577
Congress center	Congress	Kitakyushu	1991	8,997
Department store	Department store	Kitakyushu	NA	25,000
High school	High school	Kitakyushu	NA	15,348
Hotel A	Hotel	Kitakyushu	2002	NA
Hotel B	Hotel	Kitakyushu	1991	NA
Hotel C	Hotel	Akita	1988	3,287
Hotel D	Hotel	Tokyo	1981	84,774
Museum A	Art museum	Kitakyushu	1976	4,443
Museum B	Museum	Kitakyushu	2003	16,947
Shopping mall A	Shopping mall	Miyazaki	2005	28,631
Shopping mall B	Shopping mall	Kitakyushu	1981	7,000
Theater A	Art theater	Kitakyushu	2003	5,666
Theater B	Event hall	Kitakyushu	1994	3,584
University A	University	Kitakyushu	1978	NA
University B	University	Kitakyushu	1966	67,800

NA: not available.

15.2.2 Collection and Analysis of Chemicals

The concentrations of VOCs and aldehydes were measured. The chemicals were collected by a diffusive sampler in all the cases (personal exposure, indoor air, and outdoor air). A number of samplers for collecting the chemicals were set up at each sampling site so that the average indoor air condition of the area could be determined. To evaluate the personal exposure level of workers to chemicals, the personal sampler was attached to a worker's chest during working and non-working hours. After the collection, the VOC samples were stored in a freezer and the aldehyde samples were stored in a refrigerator until they were analyzed. The VOCs were analyzed as follows. An activated charcoal in a sampling tube (VOC-SD, Supelco, Sigma-Aldrich Japan) was moved to a test tube; 2 ml of carbon disulphide was added, and then VOCs were extracted. The VOCs in the extracted solution were analyzed by using a capillary gas chromatograph – mass spectrometer apparatus (Hewlett Packard, USA) with an auto sampler. The capillary column used was a 60 mm × 0.25 mm Aquatic (GL Sciences, Japan).

Aldehydes were collected by a diffusive sampler (DSD-DNPH, Supelco, Sigma-Aldrich Japan) silica gel impregnated with 2, 4-dinitrophenyl hydrazine. The aldehydes absorbed on the silica gel were extracted with 3 ml of acetonitrile. The separation and determination were performed by a high-performance liquid chromatography (HPLC) apparatus (Shimadzu LC-10 AD, Japan) using a column of Wakosil-II 5C18 HG, 250 mm × 4.0 mm (i.d.) (Wako Pure Chemical, Japan). The NO_2 absorbed by a filter (Toyo Roshi, Japan) was extracted in a solution of sulfanilic acid, phosphoric acid, and 0.1wt% N-(1-naphthyl) ethylenediamine dihydrochloride. The amount of NO_2 in the extracted solution was determined by using a UV-VIS spectrophotometer (Shimadzu UV-2200A, Japan).

15.2.3 Health Survey by Questionnaire

At the same time, as another indicator of the air quality in many of the buildings, a health survey for employees was used to investigate the incidence of multiple chemical sensitivity (MCS) and the effectiveness of the Quick Environment Exposure and Sensitivity Inventory (QEESI) (Miller and Prihoda 1999a, b) in Japanese workers. The QEESI (Japanese version) and a checklist for evaluation of fatigue were used to examine 410 workers in specific buildings.

15.3 Results

15.3.1 Indoor and Outdoor Air Quality and Personal Exposure

The characteristics of indoor and outdoor air quality in 22 public facilities are summarized in Table 15.3. To investigate the relationship between indoor and outdoor air quality, the ratio of indoor to outdoor concentrations of air pollutants were also calculated. Formaldehyde shows the highest concentration of 18.7 μg/m^3 at geometric mean (GM). Other chemicals, including acetaldehyde, toluene, xylene, ethylbenzene, decane, undecane, and limonene show relatively high concentrations of more than 5 μg/m^3 at GM. The maximum values of toluene, styrene, formaldehyde, and acetaldehyde exceed the guideline values of the MHLW, as shown in Table 15.1. However, only a few sampling points exceeded the guideline values, as shown in Figs. 15.1, 15.2, 15.3, 15.4, 15.5, 15.6, 15.7 and 15.8.

Table 15.3 Typical concentrations of air-polluting chemicals

Compounds		[a]Indoor concentration (μg/m^3) (n = 759)			[b]Outdoor concentration (μg/m^3) (n = 30)					Personal exposure (μg/m^3) (n = 332)			
		minimum	maximum	GM	minimum	maximum	GM		a/b	minimum	maximum	GM	
Aromatic hydrocarbones	Benzene	<1.43	78.79	1.89	<1.43	13.43	1.71		1.11	<1.43	71.58	1.78	
	Toluene	<0.64	737.51	8.47	<0.64	33.50	5.13		1.65	<0.64	525.59	9.39	
	Ethylbenzene	<0.56	124.16	5.10	<0.56	20.18	2.10	***	2.43	<0.56	99.21	4.28	
	m/p-Xylene	<0.91	73.44	3.85	<0.91	18.36	1.62	***	2.38	<0.91	119.14	3.83	
	o-Xylene	<2.69	69.49	3.07	<2.69	14.37	1.56	***	1.97	<2.69	86.14	3.50	
	1,2,3-Trimethylbenzene	<4.17	142.18	2.58	<4.17	ND	ND			<4.17	177.66	2.58	
	1,2,4-Trimethylbenzene	<3.43	1322.35	3.51	<3.43	14.94	2.15		1.64	<3.43	1312.94	3.68	
	1,3,5-Trimethylbenzene	<2.74	370.96	2.31	<2.74	16.25	1.62		1.43	<2.74	416.62	2.20	
	Styrene	<4.25	369.29	3.06	<4.25	ND	ND			<4.25	123.91	2.66	*
Aliphatic hydrocarbones	Heptane	<1.80	610.61	2.94	<1.80	20.14	1.60		1.83	<1.80	198.28	2.84	
	Octane	<1.68	105.52	1.86	<1.68	10.36	1.31		1.42	<1.68	353.09	2.40	**
	Nonane	<2.09	299.12	3.05	<2.09	22.49	2.09		1.46	<2.09	268.30	2.32	**
	Decane	<2.03	1059.19	8.31	<2.03	175.86	4.76		1.74	<2.03	987.78	13.56	***
	Undecane	<8.03	298.67	10.43	<8.03	63.39	9.06		1.15	<8.03	1106.21	12.52	
	2,4-dimethylpentane	<1.02	54.12	0.98	<1.02	9.24	1.05		0.93	<1.02	149.26	0.99	
Terpenes	Alpha-pinene	<5.36	311.41	1.69	<5.36	18.44	1.32		1.27	<5.36	1262.47	2.40	**
	Limonene	<5.78	270.40	5.64	<5.78	7.00	3.05	**	1.85	<5.78	333.36	9.53	***
Alcohols	1-Butanol	<0.97	74.20	1.77	<0.97	10.58	1.09		1.62	<0.97	137.14	1.73	
	2-Ethyl-1-hexanol	<1.33	172.29	1.83	<1.33	7.13	0.78	**	2.34	<1.33	450.86	1.83	
Ketones	Methyl ethyl ketone	<1.29	103.14	1.94	<1.29	7.92	1.34		1.45	<1.29	39.53	2.16	

Table 15.3 (continued)

Compounds		aIndoor concentration (μg/m³) (n = 759) minimum	maximum	GM	bOutdoor concentration (μg/m³) (n = 30) minimum	maximum	GM	a/b	Personal exposure (μg/m³) (n = 332) minimum	maximum	GM
	Methyl isobutyl ketone	<2.29	44.26	1.49	<2.29	12.27	1.29	1.16	<2.29	37.48	1.57
Chlorinated organic compounds	Carbon tetrachloride	<1.12	232.99	1.01	<1.12	13.08	1.04	0.98	<1.12	83.95	1.15
	1,2-Dichloroethane	<0.84	17.11	0.49	<0.84	14.92	0.54	0.90	<0.84	131.43	0.50
	1,2-Dichloropropane	<0.87	9.54	0.45	<0.87	ND	ND		<0.87	ND	ND
	p-Dichlorobenzene	<1.07	223.49	2.96	<1.07	54.22	1.65	1.79	<1.07	600.63	7.01 ***
	Trichloroethylene	<1.38	11.15	0.82	<1.38	3.75	0.87	0.94	<1.38	4.56	0.74
	Tetrachloroethylene	<1.47	83.25	1.13	<1.47	7.11	0.70	1.62	<1.47	78.32	0.75
	1,1,1-Trichloroethan	<2.16	8.52	1.15	<2.16	ND	ND		<2.16	15.01	1.14
	Dibromochloromethane	<0.84	40.03	0.45	<0.84	8.91	0.47	0.96	<0.84	158.00	0.48
	Chloroform	<1.35	50.45	1.18	<1.35	8.86	1.10	1.08	<1.35	79.89	1.23
Esters	Ethyl acetate	<2.16	491.98	2.62	<2.16	14.14	1.46	1.80	<2.16	1491.58	4.08 ***
	Butyl ester acetic acid	<2.18	281.77	2.40	<2.18	9.68	1.79	1.34	<2.18	462.70	4.32 ***
Aldehydes	Formaldehyde	<1.92	128.24	18.67	<1.92	38.18	9.16 ***	2.04	<1.92	218.60	28.88 ***
	Acetaldehyde	<1.42	134.79	9.45	<1.42	12.59	3.32 ***	2.85	<1.42	128.40	15.29 ***
Total VOCs		47.7	2686.44	214.43	39.07	300.42	101.19 ***	2.12	54.32	3087.52	293.83 ***

GM; Geometric mean. * $P<0.05$, ** $P<0.01$, *** $P<0.001$ compared to Indoor concentration.

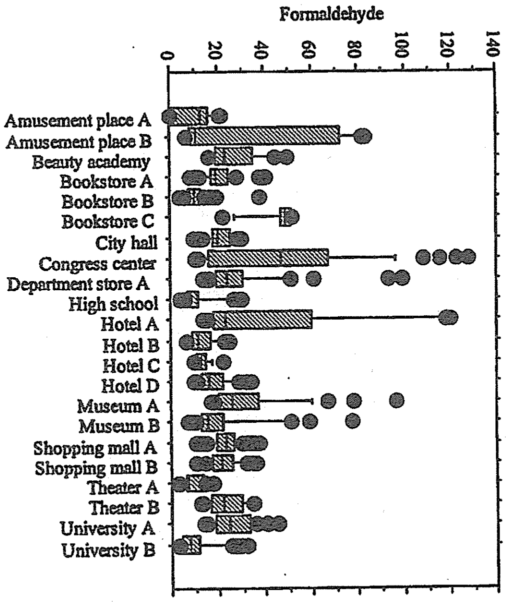

Fig. 15.1 Distribution of formaldehyde concentrations (μg/m³) in various buildings

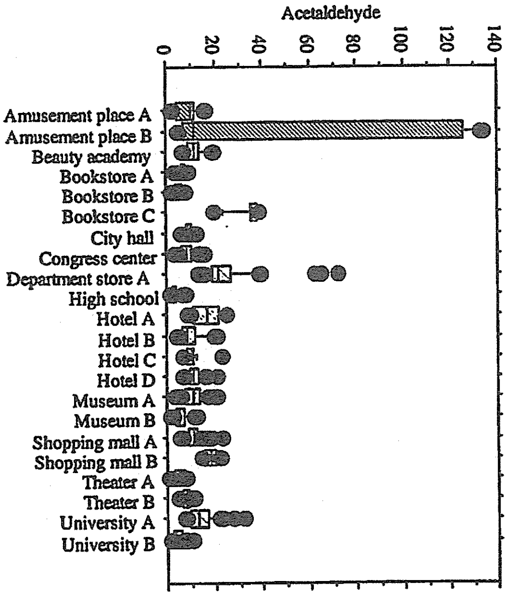

Fig. 15.2 Distribution of acetaldehyde concentrations (μg/m³) in various buildings

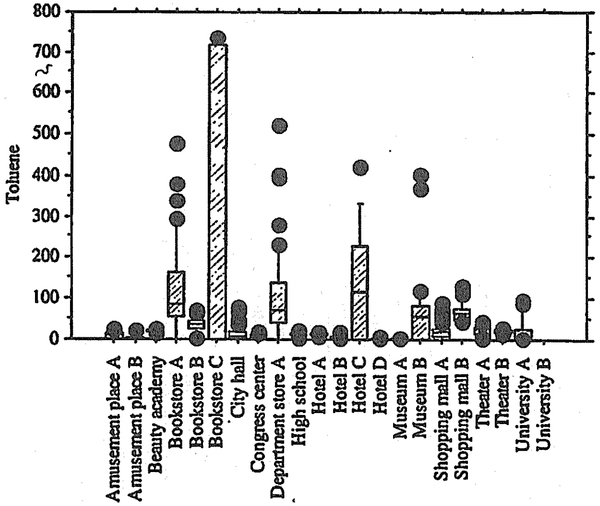

Fig. 15.3 Distribution of toluene concentrations (μg/m^3) in various buildings

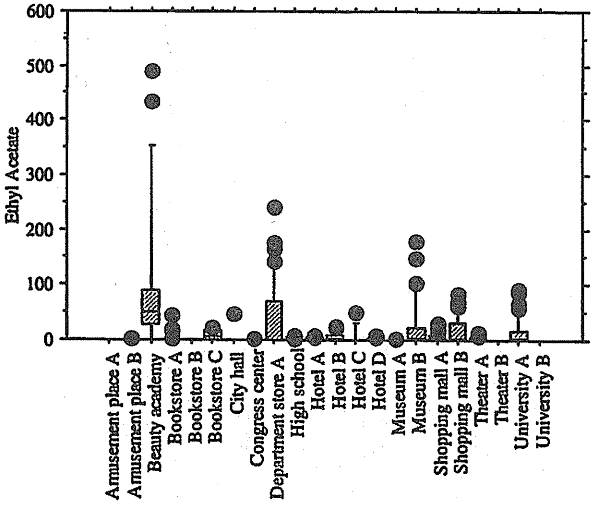

Fig. 15.4 Distribution of ethyl acetate concentrations (μg/m^3) in various buildings

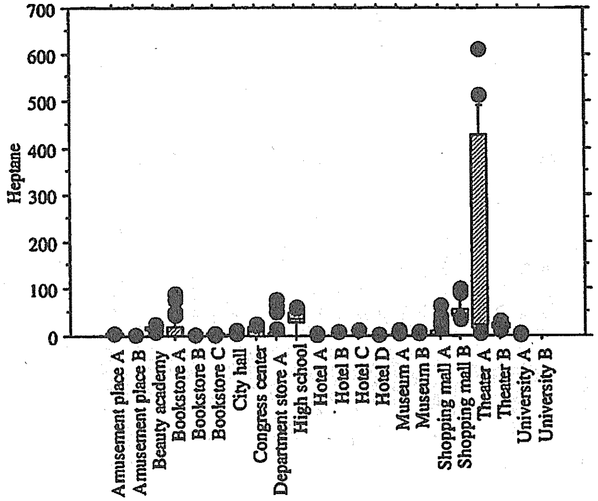

Fig. 15.5 Distribution of heptane concentrations (μg/m^3) in various buildings

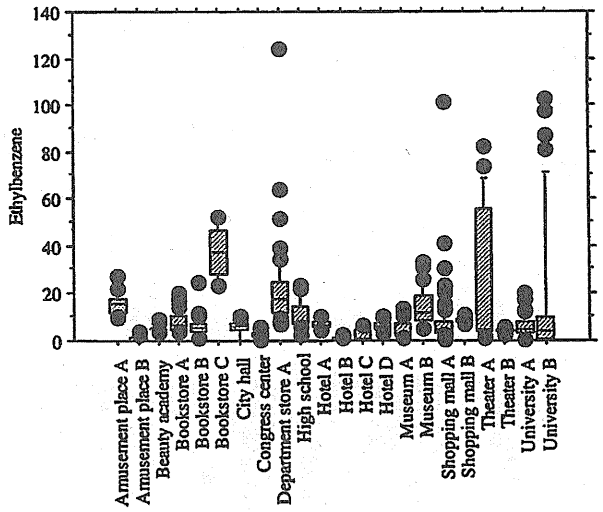

Fig. 15.6 Distribution of ethylbenzene concentrations (μg/m^3) in various buildings

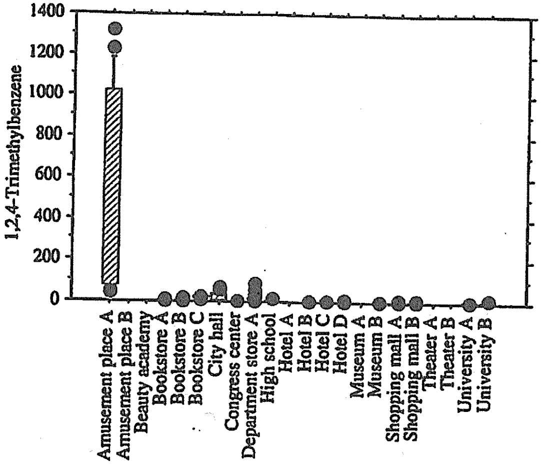

Fig. 15.7 Distribution of 1,2,4-trimethylbenzene concentrations (μg/m^3) in various buildings

Most of the chlorinated organic compounds show very low indoor concentrations. Excluding p-dichlorobenzene and tetrachloroethylene, the ratios of indoor to outdoor concentrations were almost all one or lower. On the other hand, other chemicals, especially aromatic hydrocarbons, showed a high indoor-to-outdoor ratio, suggesting indoor emission sources for these compounds.

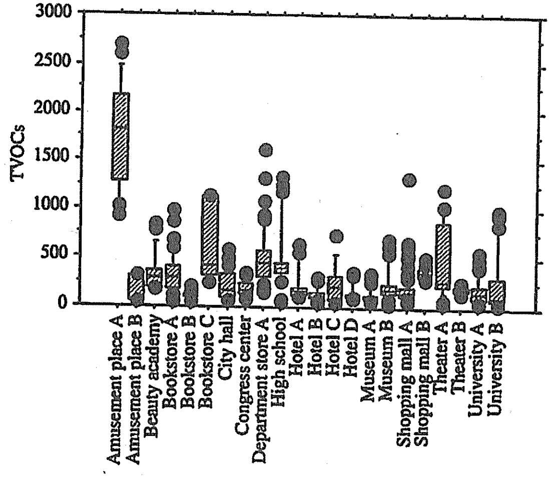

Fig. 15.8 Distribution of total VOC (TVOC) concentrations (μg/m^3) in various buildings

15.3.2 Characteristics of Air Quality and Specific Chemicals at Each Public Building

Distributions of the concentrations of specific chemicals and total VOCs (TVOCs) in various buildings are shown in Figs. 15.1, 15.2, 15.3, 15.4, 15.5, 15.6, 15.7 and 15.8 by box and whisker charts. The bottom, mid-line, and top of the box indicate the 25th percentile, median, and 75th percentile, respectively. The whiskers show the 10th and 90th percentiles.

In Figs. 15.1 and 15.2, amusement facility B showed relatively high indoor aldehyde concentrations during work hours, especially acetaldehyde, which was much higher than during non-work hours and in outdoor air (data not shown). Amusement facility B is a pachinko parlor that permitted guests to smoke. The parlor was 50% full when we investigated (about 150 customers were playing). Cigarette smoke may cause the high concentration of aldehyde in this location. Because this building has less than 3,000 m^2 of floor space, it is outside the scope of the Act on Maintenance of Sanitation in Buildings. Thus, ventilation standards are not enforced for this building. As shown in Fig. 15.1, few measurements at other buildings, including the Congress Center and hotel A, showed high concentrations (over 100 μg/m^3) of formaldehyde.

Figure 15.3 shows that the toluene concentration is high in some public buildings, especially in small bookstore C, which is also outside the scope of the Act on Maintenance of Sanitation in Buildings. The major source of toluene is considered to be printing inks used in books. Compared to other VOCs, toluene and ethylbenzene were generally detected in very high concentrations at bookstores. Large bookstores A and B also showed high concentrations of toluene, but these values are significantly less than the value of bookstore C. Because bookstores A and B have over 3,000 m^2 of floor space, ventilation standards are enforced in these buildings. In all the other buildings except department store A, hotel C, and museum B, all measurements were below the guideline values.

As shown in Fig. 15.4, ethyl acetate was detected in relatively high concentration in the beauty academy, and the concentration of butyl ester acetic acid was also relatively high. These tendencies were observed at the barber shop and beauty parlor in a university hospital, suggesting the influence of hair-dressing and cosmetic materials. At theater A, some sampling points show high concentrations of heptane (Fig. 15.5), ethylbenzene (Fig. 15.6), butanol, octane, tetrachloroethylene and methyl isobutyl ketone, these probably arise from many components, such as the carpeting, wall, and furniture.

The air quality of a bowling alley was measured (amusement place A). Of the VOCs, the concentrations of benzene (data not shown), toluene (Fig. 15.3), and xylene (data not shown) were all low, whereas those of nonane, decane, and undecane were relatively high (data not shown), and trimethylbenzene was found in very high concentration (Fig. 15.7). The personal exposure level showed the same trend as that of indoor air, and the level during work hours was higher than that during non-work hours. The high concentrations of some VOCs may come from wax on the alley and floor.

We measured air quality at department store A, a seven-story building with a total floor area of 25,000 m^2. Different VOCs were detected on each floor. Many kinds of VOCs, including toluene, ethyl acetate, ethylbenzene, methylethylketone, p-dichlorobenzene, styrene, limonene, and benzene, showed higher concentrations during work hours compared to other buildings. This may be due to the many kinds of merchandise sold at the department store.

The styrene concentration was less than the guideline value in almost all the places we investigated. Only two samples in the department store showed higher concentrations of p-dichlorobenzene than the guideline value. This may be due to the presence of moth repellents and air fresheners.

The Japanese government established a standard for NO_2 in the outdoor environment of 40–60 ppb for 1 day's average 1-h value. Only a few measurements showed a higher value than the environmental air quality standards. Specifically, NO_2 was observed at high concentrations in places where combustion tools were used, such as the restaurant in the department store (data not shown).

We also measured physical parameters (data not shown) such as temperature, relative humidity, noise, wind velocity, illumination, and particulate matter concentration in the buildings and found that those parameters were generally at an appropriate level except in the pachinko parlor. There, particulate matter exceeded the standard level, probably due to the smoking by customers, and the noise level was high, due to the nature of the gaming device.

15.3.3 Comparison of Indoor Air Quality and Personal Exposure

Of the aldehydes, the concentration of formaldehyde was twice as high as that of acetaldehyde in all measurements. The personal exposure level of about 80–90% for these aldehydes was parallel to that of indoor air. However, the personal exposure level of 10 ~ 20% for the remainder was obviously higher than the indoor concentration (Fig. 15.9). This is thought to reflect the influence of activities of individuals, including smoking, and factors in the working environment, such as working near emission sources.

Personal exposure to these two aldehydes in non-work hours (mostly spent at home) was higher than that in work hours (at the office), as shown in Fig. 15.10. These results suggest that there are more emission sources at home than at the office. Alternatively, the ventilation system required by the Act on Maintenance of Sanitation in Buildings has decreased the density of aldehyde concentrations in the office.

15.4 Discussion

15.4.1 Characteristics of Air Quality in Japanese Public Buildings

By using diffusive samplers, we were able to measure 32 kinds of VOCs, formaldehyde, and acetaldehyde. The indoor air quality in the large public buildings we investigated was maintained in good condition. This might be due to Japanese legal requirements that administrators of large buildings meet ventilation standards and regularly measure the indoor air environment in accordance with the Act on Maintenance of Sanitation in Buildings. Depending on the nature of the buildings, however, the kind and concentration of VOCs varied. Most sampling points in the buildings did not exceed the guideline values for formaldehyde (100 μg/m^3) and

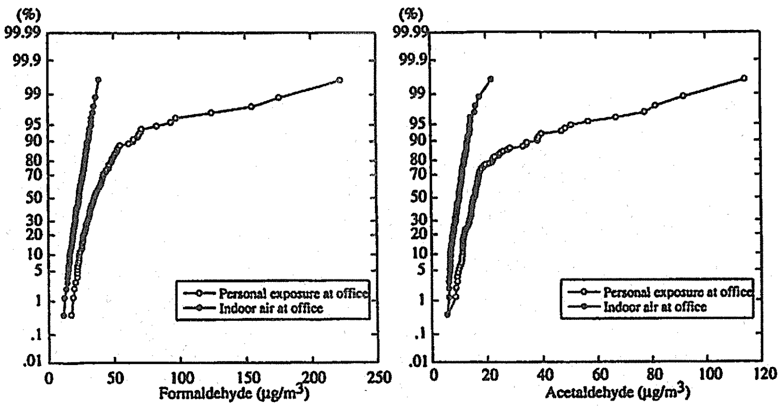

Fig. 15.9 Cumulative frequency distribution for formaldehyde (*left*) and acetaldehyde (*right*) concentrations. *Open and closed circles* show personal exposure during working hours and indoor air concentration at office, respectively

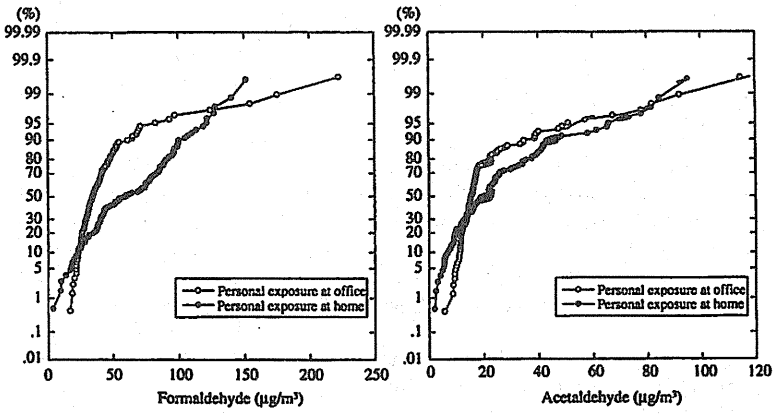

Fig. 15.10 Cumulative frequency distribution for formaldehyde (*left*) and acetaldehyde (*right*) concentrations. *Open and closed circles* show personal exposure during working hours (at office) and non-working hours (at home), respectively

acetaldehyde (48 $\mu g/m^3$), suggesting that the indoor air quality of all the buildings is good in terms of pollution by aldehydes.

The total VOCs in some buildings showed high concentrations (Fig. 15.8). The toluene in bookstores may come from printing ink used in books. The trimethylbenzne in the bowling alley (amusement place A) was considered to come from wax on the floor. The managers of these buildings may need to consider better ventilation.

Overall, air quality in various large buildings and employees' personal exposure levels were relatively good, especially for chemicals that have guideline levels set by the MHLW. However, we must note that there were some exceptional cases, such as toluene in bookstores and aldehyde and noise in the pachinko parlor.

15.4.2 Characteristics of Air Quality in Japanese Individual Houses

On the other hand, what is the indoor air quality in individual houses in Japan? Recently, Osawa and Hayashi reported the status of chemical pollution of indoor air in Japanese houses based on a nationwide field survey from 2000 to 2005 (Osawa and Hayashi 2009). A survey in 2000 revealed that the indoor concentrations of formaldehyde and toluene exceeded the guidelines shown in Table 15.1 in more than 27 and 12% of the houses surveyed, respectively. These results led to the development of various countermeasures for improving the indoor air environment, such as amending the Building Standard Law (BSL) to a performance-based regulation and enacting the Housing Quality Assurance Act, which provides a housing performance indication system. These countermeasures decreased the levels of indoor chemicals, especially formaldehyde and toluene, year by year, as shown in Fig. 15.11. In addition to improvements in building materials and the new installation of continuous ventilation systems under the amended BSL, these successes depend on many efforts for the improvement of indoor air quality by the government, private construction companies, manufacturers of building materials, and various other interested parties.

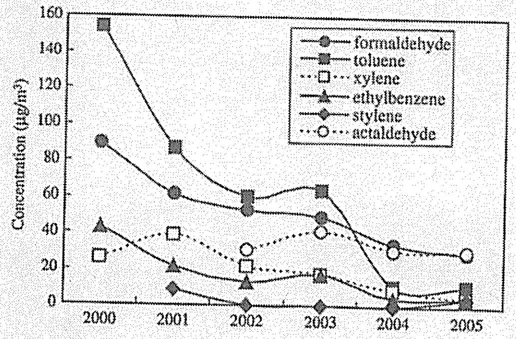

Fig. 15.11 Changes in the indoor concentration of VOCs in Japanese houses

In addition, the countermeasures are ongoing, expanding the target from formaldehyde, a major pollutant at the time, to other VOCs and microbial volatile organic compounds (MVOCs) (Kilburn 2009; Kishi et al. 2009; WHO 2009).

While the changes in severe sick house problems in our country such as rapid air tightening, and heavy use of pollutant-emitting materials are not necessarily shared in other countries, changes in the residential environment are shared across hot and humid East Asia. Therefore, understanding and evaluation of housing conditions is expected to have considerable application in the future.

15.4.3 Questionnaire Survey of Workers by QEESI

Three criteria used in the QEESI (symptom severity, chemical intolerance, and other intolerance) were evaluated in this study (Hojo et al. 2009). Clinical histories were also surveyed. Responses were obtained from 368 (89.8%) of 410 workers (Manabe et al. 2008).

The results showed that 132 individuals (35.9%) have been diagnosed as having allergies. Only two individuals (0.5%) were found to be MCS patients, and none were SBS patients. Applying the "high" criteria of the QEESI to the standard of Miller and Prihoda (1999a, b), we determined that only four individuals (1.1%) met all three criteria, and 17 individuals (4.6%) met two of the three criteria, as shown in Fig. 15.12 . These values are the same as the values in previous Japanese reports (Hojo et al. 2008; Katoh et al. 2007) and less than those reported by Miller and Prihoda (1999a, b).

The QEESI score of allergic persons was higher than that of non-allergic persons (Fig. 15.13). Among non-allergic persons, those who scored high for accumulation

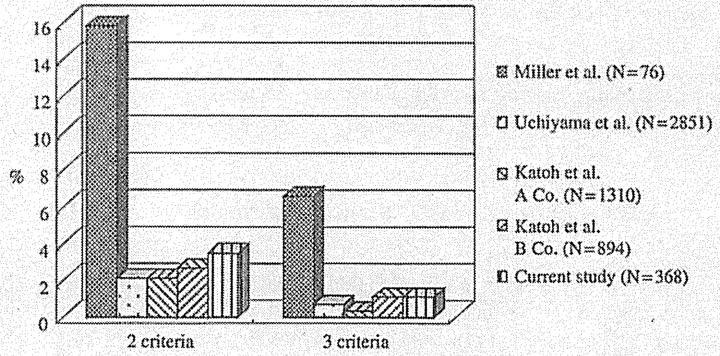

Fig. 15.12 Proportion of subjects who met two or three criteria (symptom score, chemical intolerance score, and other intolerance score) of the QEESI questionnaire

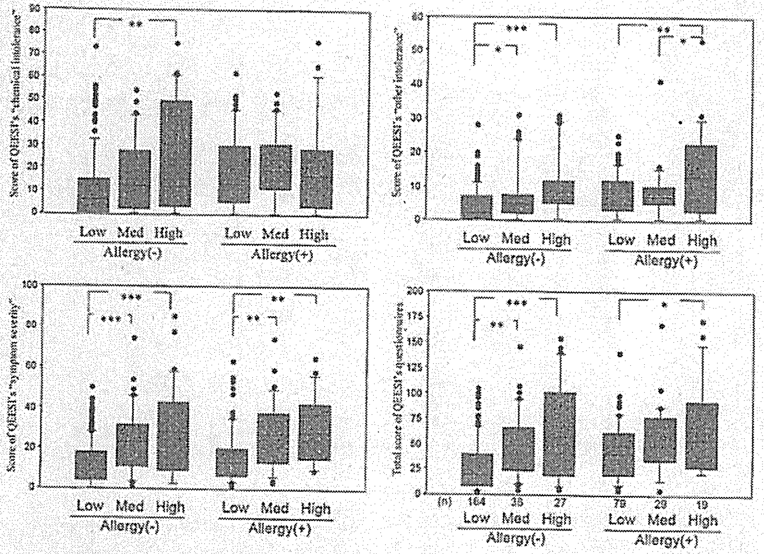

Fig. 15.13 Relationship of allergy and work load to QEESI score (chemical intolerance score, symptom score, and other intolerance score). *Low, Med* and *High* indicate the workload assessed by a checklist on the accumulation of fatigue developed by the Ministry of Health, Labor, and Welfare, Japan

of fatigue in the checklist showed a high score in the QEESI. These findings indicate that the QEESI score tends to increase with workload and to be high in individuals with allergies. Therefore, careful consideration is required when QEESI is used to screen MCS patients in Japan.

15.4.4 Aldehyde Concentration Under Specific Circumstances in Medical Laboratories

The concentration of formaldehyde is quite high under specific circumstances, including in medical laboratories. Formaldehyde is widely used during disinfection procedures or embalming of bodies in the medical field. Medical students are exposed to formaldehyde during their dissection course. First, we evaluated formaldehyde exposure that occurred in a gross anatomy laboratory with a general ventilation system. Formaldehyde in the air was sampled by an active 2,4-dinitrophenylhydrazine (DNPH)-silica gel cartridge, extracted with acetonitrile, and analyzed by HPLC. The GM formaldehyde concentration was 20–93 ppb in the anatomy laboratory before dissection began. After dissection began, the highest GM concentrations were 1,011–1,380 ppb (Kunugita et al. 2004). This suggests

we should reduce formaldehyde exposure for medical students and lecturers during gross anatomy dissection courses. Next, we improved the ventilation by using a local ventilation system that included the existing ventilation assigned to the laboratory and a newly developed local ventilation apparatus for each dissection table. After these improvements, the GM concentrations were 100 ppb or less (Yamato et al. 2005). Significant decreases were also observed in symptoms of thirst, burning eyes, itchy eyes, feeling uncomfortable, and fatigue during exposure compared with the symptoms before the ventilation system was improved.

15.4.5 Biological Evaluation in Mice Exposed to Low Dose of Chemicals

To understand the effect of low dose exposure of VOCs on neuro-immuno-endocrine networks, we have studied many kinds of animal experiments (Ahmed et al. 2007a, b; Fujimaki et al. 2004a, b, 2007; Hayashi et al. 2004; Sari et al. 2004, 2005; Tsukahara et al. 2006; Win-Shwe et al. 2010a, b; Yamamoto et al. 2009). Our study showed that long-term exposure to low level of formaldehyde and the allergic condition induced by OVA sensitization may act to the hypothalamo-pituitary-adrenal gland (HPA)-axis as a stressor (Hayashi et al. 2004; Sari et al. 2004, 2005). Exposure to 80 and 400 ppb formaldehyde significantly increased the brain NGF levels in the OVA immunized mice (Fujimaki et al. 2004a). We have also demonstrated that low-level toluene and formaldehyde exposure affects memory function-related gene expression in the hippocampus of C3H/HeN mice (Ahmed et al. 2007a, b).

Long term exposure to low levels of VOCs including formaldehyde and toluene can disturb normal homeostatic response to enhance neural network, and coadministration with immunological stimuli can activate it abnormally, resulting in induction of neurogenic and immunogenic inflammation in the brain.

15.5 Conclusions

The indoor air quality in large public buildings we investigated was maintained in good condition. The level of personal exposure generally showed the same tendency as the indoor air pollution level. This might be due to the Japanese legal requirements that administrators of large-scale buildings meet ventilation standards and regularly measure the indoor air environment in accordance with the Act on Maintenance of Sanitation in Buildings. Although the lifestyle and engineering methods used in indoor and outdoor structures are not similar elsewhere, the living environment has changed in similar ways in many countries. Therefore, understanding and evaluating these conditions is expected to have considerable application in the future.

The basis of indoor air quality control is suppressing pollutants at the source by regulating materials and eliminating pollutants by securing ventilation. Neither of these measures alone is sufficient; both must be used in good balance within technological and economic restrictions.

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