1. Introduction

p-Dichlorobenzene (1,4-dichlorobenzene; CAS Registry No. 106-46-7, hereafter referred to as pDCB) was first produced commercially in the U.S.A. in 1915 (IARC, 1982). It has long been used as a moth repellent and as a space deodorant; it is also used industrially as an intermediate in organic syntheses.

The pDCB that is found in indoor air originates mainly from moth repellents used to protect clothing and from deodorants that are used in the household. The pDCB that is existing indoor, while providing benefits such as moth control and deodorizing effects, raise some concerns regarding potential risks to human health. We focused our risk assessment on human exposure through inhalation of pDCB in indoor air because pDCB is mainly used as a moth repellent to protect clothing,. Our primary objective was to estimate the magnitude of risks from the present uses of pDCB by examining and analyzing knowledge regarding exposures and potential hazards. Our secondary objective was, in the event of a significant risk being identified, to suggest possible actions that might be adopted, taking into account the risk–benefit tradeoff. In estimating the risks, we investigated whether hazards observed in animal experiments were likely to occur in humans, and we estimated the distributions of mid- to long-term exposure concentrations from monitoring data, which were derived from short-term measurements.

pDCB exists as white, volatile crystalline material with a distinctive aromatic odor (Merck, 2001). Amoore & Hautala (1983) claim that most people can detect the odor of pDCB at a concentration of 1 mg/m^3 in air or 0.011 mg/L in water. pDCB dose not occur naturally, but is produced by chemical companies (ATSDR, 1998).

Table 1 shows the quantities of pDCB produced, traded, and consumed in Japan, sorted by the type of use. Because pDCB occurs in the solid state at room temperatures and undergoes sublimation, it is commonly used in households and public facilities as a moth repellent for clothing and as a deodorant for toilets. Table 2 summarizes the total usage of moth repellents and deodorants and the quantities consumed by general households and businesses. The types of establishment that make widespread use of moth repellents and deodorants are laundry services, hotels, offices, and schools.

Table 1. Quantities of pDCB Produced, Imported, and Exported, and the Usage of pDCB in Japan (Units: t)

FY	Production and Trade			Quantities Consumed (by use)	
	Domestic	Import	Export	Moth repellent /Deodorant	Industry
1979 1)	27,500	—	—	—	—
1998 1)	36,500	7,500	—	21,000	23,000
1999 1)	35,100	8,900	—	20,000	24,000
2000 1)	39,500	8,500	—	20,000	28,000
2001 2)	32,500	7,500	0	20,000	20,000 4)
2002 3)	—	—	—	18,000	—

1) Source: Japan Society of Insect Repellants on Textile Products.

2) Source: National Institute of Technology and Evaluation (2003).

3) Source: Ministry of Economy, Trade and Industry, Ministry of the Environment (2004).

4) This includes 18,000 t used in manufacturing resins and 2000 t used as intermediates in producing other products (agrochemicals and resin additives).

* : Data not available.

Table 2. Consumers of Fumigants and Deodorants, and Estimated Quantities Consumed (Units: t)

FY	Moth repellent		Deodorants		Total	Source
	Household	Industry	Household	Industry		
1997	17,010	1,890	1,050	1,050	21,000	Ministry of the Environment (1999)
1998	17,010	1,890	1,050	1,050	21,000	Ministry of the Environment (2000)
1999	16,200	1,800	1,000	1,000	20,000	Ministry of Economy, Trade and Industry, Ministry of the Environment (2001)
2000	16,200	1,800	1,800	200	20,000	Ministry of Economy, Trade and Industry, Ministry of the Environment (2002)
2001	18,000		2,000		20,000	Ministry of Economy, Trade and Industry, Ministry of the Environment (2003)
2002	17,100		900		18,000	Ministry of Economy, Trade and Industry, Ministry of the Environment (2004a)

2. Hazard Assessment

Comprehensive hazard assessments on pDCB have been conducted by the European Union (2004), The Agency for Toxic Substances and Disease Registry (ATSDR; 2004), The US Environmental Protection Agency (US EPA; 2003), The Netherlands National Institute for Public Health and the Environment (RIVM; 2001), the Australian National Industrial Chemicals Notification and

Assessment Scheme (NICNAS; 2000), the Japanese Ministry of Health and Welfare (2000), the ATSDR (1998), the Japan Society for Occupational Health (1998), the Experts' Meeting on Household Articles in Japan (1997),the US EPA (1996), and the World Health Organization/International Programme on Chemical Safety (WHO/IPCS) (1991). Qualitative carcinogenicity evaluations have been conducted by The US National Toxicology Program (NTP) (2005) and the International Agency for Research on Cancer (IARC) (1999).

Although we assumes that inhalation is the main route of exposure to pDCB, this document contains a comprehensive review of hazard-assessment information, including oral exposures, and summarizes its rationale in the reference concentration, for chronic inhalation hazards, which was determined by Research Center for Chemical Risk Management, National Institute for Advanced Industrial Science and Technology (CRM, AIST).

The endpoint of the assessment of the toxicity hazard of chronic exposure to pDCB was hepatotoxicity. Hepatotoxity was observed in test animals exposed to pDCB by both oral and inhalation routes; increases in liver weight, increases in leakage of enzymes in the liver, and histopathological changes were also observed.

After results of some chronic inhalation studies were examined in detail, a high-quality two-year study in mice was chosen as the study on which to base the reference concentration. Non-neoplastic changes observed in the livers of mice in this study were defined as an endpoint, and the no observed adverse effect level (NOAEL) was calculated to be 80 mg/m^3 by converting the study result of 75 ppm into an equivalent concentration at a continuous exposure of 24 hours/day.

The considerations regarding other endpoints included the following. With regard to eosinophilic changes of the olfactory epithelium in female rats, the total number and frequency of moderate and serious occurrences increased. However, these are natural types of changes, as they were also observed in all the control animals at the final autopsy. Metaplasia found in nasal cavities was determined to be irrelevant to eosinophilic changes in the olfactory epithelium, and is therefore not an apparent toxic effect.

With regard to the carcinogenicity of pDCB, increases in the incidence of neoplasm were observed in carcinogenicity studies in rodents. These included an increase in the incidence of renal tumors in male rats and an increase in the incidence of hepatic tumors in mice. For reasons given below, however, we concluded that extrapolation of these results to humans is inappropriate. The increase in the incidence of renal tumors in male rats was considered to be a phenomenon specific to

$\alpha 2 \mu$-globulin-related reactions, and is therefore irrelevant to humans. This judgment was consistent throughout the existing hazard assessment reports. The mechanism for increased incidence of liver tumors in mice is believed to be a reaction that shows a threshold exposure, because pDCB can be judged to be a nongenotoxic substance despite the fact that it induces cell proliferation accompanying liver-cell division in mice. In addition, the majority of the existing hazard assessments suggest the existence of a threshold exposure for liver tumors in mice. The mice used in the tests (B6C3F1, BDF1) show a high incidence of spontaneous occurrence of hepatic adenoma and carcinoma. Moreover, the metabolism of pDCB in the liver differs greatly among species. Compared with humans, the mouse is a highly sensitive species. As a result, it was concluded that the liver-tumor outcome observed in mice could not be extrapolated to the assessment of the incidence of liver tumors in humans.

3. Emissions of pDCB to the Environment

The survey by the Pollution Release and Transfer Registry (PRTR, Japan) found that most of the pDCB released to the atmosphere comes from moth repellents and deodorants used in households (18,000 t in the fiscal year 2002, amount of emissions out of the reported quantities). PRTR also estimated emissions from moth repellents and deodorants used in households for individual prefectures. The amount of usage of moth repellents in households and the doses recommended by manufacturers of pDCB-based moth repellents are summarized. Moth repellents are used in more than 90% of households and pDCB-based moth repellents are used 40–50% of them.

Emissions from industrial facilities, which can be considered as specific to particular limited areas where pDCB manufacturing, resin production processes, and processes relevant to pDCB emissions are carried out, are summarized and the quantities of emissions from the industrial facilities that were reported in the PRTR survey are presented. Facilities that reported on their pDCB emissions were classified by the type of industry: most fell within the classification “manufacturing industry”, which includes “chemical industry”. In the fiscal year 2002, PRTR-reported emissions of pDCB were 81 t (more than 99% of which was released to the atmosphere) and PRTR-reported transfers of the substance were 111 t.

4. Concentrations in Indoor Air

pDCB concentrations in indoor air, as reported in the existing literature, are summarized. A number of surveys have been conducted on various scales throughout Japan, and the measured concentrations were found to vary among the surveys. The arithmetic means of the indoor concentrations were around 50 to 350 $\mu g/m^3$, and the medians were around 3 to 25 $\mu g/m^3$. No significant differences were found between seasons, types of housing (single-family houses or complex housing), or structures of housing. The data were also classified as to whether or not such products such as moth repellents were used.

In addition to indoor concentrations in dwellings, data from workplaces and schools are also summarized: however, the sample sizes are small.

Outcomes of studies of individual exposure levels (quantities) and biomarkers (blood or urine pDCB concentrations, and urine concentrations of 2,5-dichlorophenol, the principal metabolite of pDCB) from the existing literature are summarized. If the poor representativeness of the samples and the large variations among individuals with respect to exposure levels is taken into account, the data have limited validity for use in investigating the state of exposure.

Next, with the focus on concentrations in living rooms and other “living” spaces, raw data from “Nationwide Survey on Volatile Organic Compounds in Indoor Air” (Ministry of Health and Welfare 1999) were analyzed. From the result of this analysis, the proportion of households using pDCB-based moth repellents/fumigants was determined to be 0.9 and the proportion of households not using it was 0.1 (this group of households was called “households with no indoor usage”(abbreviated as N)). Furthermore, according to the histogram for concentrations contributed by indoor sources of emission ([indoor concentration] – [outdoor concentration]), households using pDCB-based moth repellents/fumigants could be classified into “households with higher indoor usage” and “households with lower indoor usage” (ratio 0.61:0.39). By assuming that each group has a lognormal distribution, a geometric mean (GM) and a geometric standard deviation (GSD) were obtained followed by goodness-of-fit test to the histogram. Thus, distributions of concentrations contributed by indoor emission sources in “living spaces” were obtained for each of the three groups “households with higher indoor usage”(abbreviated as H), “households with lower indoor usage”(abbreviated as L), and “households with no indoor usage”(N) (Fig. 1). The GM ($\mu g/m^3$) values were 60.7, 2.1, and 0, respectively, and the GSD values were 5.1, 3.2, and 1, respectively; the ratio of the three types of household groups was 0.55:0.35:0.10. Next, distributions of concentrations (arising from indoor sources of emission) throughout indoor spaces, including bedrooms, were estimated under the assumption that concentration of a bedroom is an average of two times as a living room at the house. Thus, the average concentration within a house was calculated, taking into account the time that individual family members spent indoors, . Table 3 shows the concentrations (GM) and GSD contributed by indoor sources of emission determined by this method. If the total indoor concentrations should be obtained, Outdoor concentrations were added to these concentrations.

Furthermore, a simple steady-state model was assumed and indoor concentrations were estimated by the model. Indoor concentrations were calculated on the basis of a supposedly valid set of parameters and the outcome was compared with the average value obtained from concentration distributions based on actual measurements. This revealed that the value based on the model was about three times higher in living spaces and 1.5 times higher in bedrooms. The cause of this discrepancy was investigated.

The results for personal exposure levels measured by Ministry of Health and Welfare (1999) were also analyzed: in this analysis, no relationships were identified between indoor concentrations and personal exposure levels. Thus, distributions of personal exposure levels were not appropriate for taking into account in the risk assessment, because adequate data could not be obtained to identify causal relationships showing e.g. when or how personal exposure levels increased. It was therefore inappropriate to include such exposure-level distributions in an analysis that would contribute to risk-reduction measures.

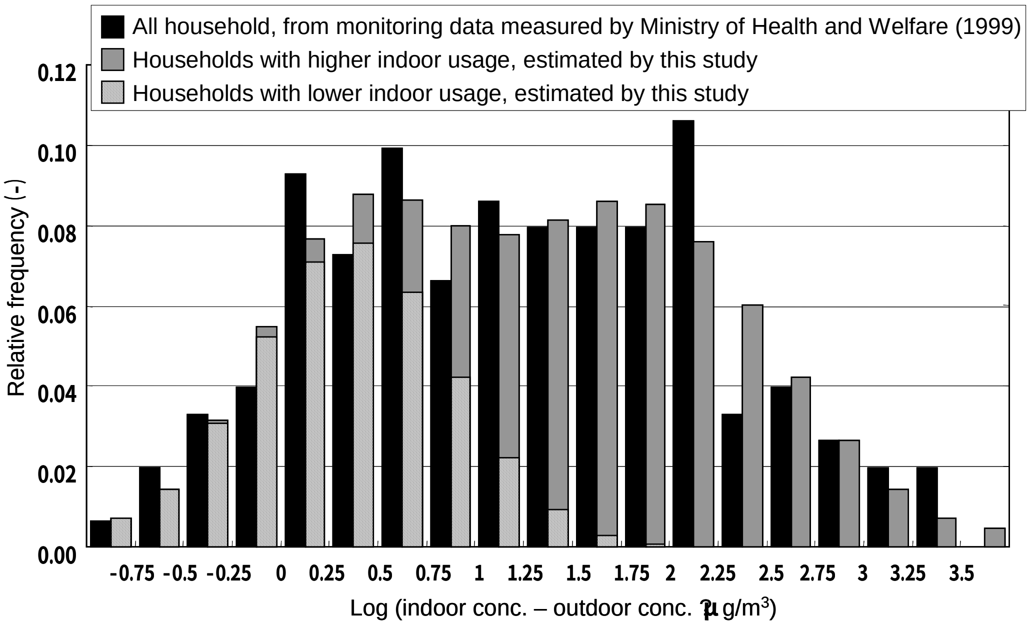

Figure 1. The histogram of the indoor concentrations in "living spaces" contributed by indoor sources of emission. The histograms of households with higher and lower indoor usage were obtained in this study. For the details of estimation method, see the text (Table IV-20).

Table 3. The indoor concentrations (GM) and GSD contributed by indoor sources of emission, determined by in relation to the times that family members spend at their residences. [1)]

Type of pDCB usage in rooms / Patterns of time spent	Households with higher indoor usage (H)		Households with lower indoor usage (L)	
	GM (μ g/m^3)	GSD	GM (μ g/m^3)	GSD
People spending at home long time (LT) [2)]	83.8	5.18	2.6	3.26

People spending at home short time (ST) 3)	94.6	5.24	3.3	3.32

1) It is assumed that the distributions of each household follows a lognormal distribution.
2) Housewives, babies, preschool children, elderly persons, and so on.
3) Working persons and students, and so on.

5. Concentrations in the Environment

Most of the reported concentration levels of pDCB in the ambient air were in the range 0.1 to several μ g/m^3.

The concentrations in the atmosphere were estimated by using several models: the AIST-ADMER (National Institute of Advanced Industrial Science and Technology - Atmospheric Dispersion Model for Exposure and Risk Assessment) was used to estimate the average concentrations in 5×5 km area (5-km mesh) and the METI-LIS model (Ministry of Economy, Trade and Industry - Low Rise Industrial Source Dispersion MODEL) was used to estimate concentrations in areas surrounding industrial facilities. The ambient air concentration levels estimated by the AIST-ADMER fell within the range 0.1 to several μ g/m^3; these values are of the same order of magnitude as those obtained by actual measurements. However, the correlation between the actual measurements and the estimates was not necessarily good. Nonetheless, it was decided to use this model to estimate ambient air concentrations, and the resultant data are to be used in the exposure evaluation in Chapter IV of this study. The reason that we decided that the model could be used was that, as mentioned in Chapter IV, indoor concentrations of pDCB were markedly higher than those in the atmosphere, and therefore errors in predicting the ambient air concentrations should not significantly affect the overall exposure evaluation.

An estimate using the AIST-DMER model was conducted using as input data the quantities of moth repellents and deodorants used throughout the county in 2002 and the PRTR-reported emission quantities in the fiscal year 2002. The mesh that showed the highest concentration, approximately 4.3 μ g/m^3, was in the Kanto region. No concentration averaged over a region (e.g. Kanto, Tohoku, etc.) exceeded 1 μ g/m^3.

The 5-km meshes that contained industrial facilities that had reported emissions to the atmosphere in the 2002 PRTR survey showed similar concentrations levels of pDCB to those for meshes that contained no such facilities. Figure 2 presents the AIST-ADMER-based estimates of ambient air concentrations of pDCB and the numbers of people exposed to each concentration level. In estimates of the ambient air concentrations of pDCB throughout Japan, the median was 0.42 μ g/m^3 and the arithmetic mean was 0.79 μ g/m^3 (both data are weighted by night-time population).

Estimated values from the METI-LIS model were very consistent with tendencies found among the actual measurements. Concentrations for the areas surrounding the business facilities that had reported the largest quantities of emissions in the PRTR survey were estimated. The results showed that concentration levels outside the boundaries of the facilities showed a yearly average of 10 to several tens of μg/m^3. From this result, we concluded (in the exposure evaluation in Chapter VI in this document) that there is no need to make detailed analysis and estimation of exposure levels for residents in these areas.

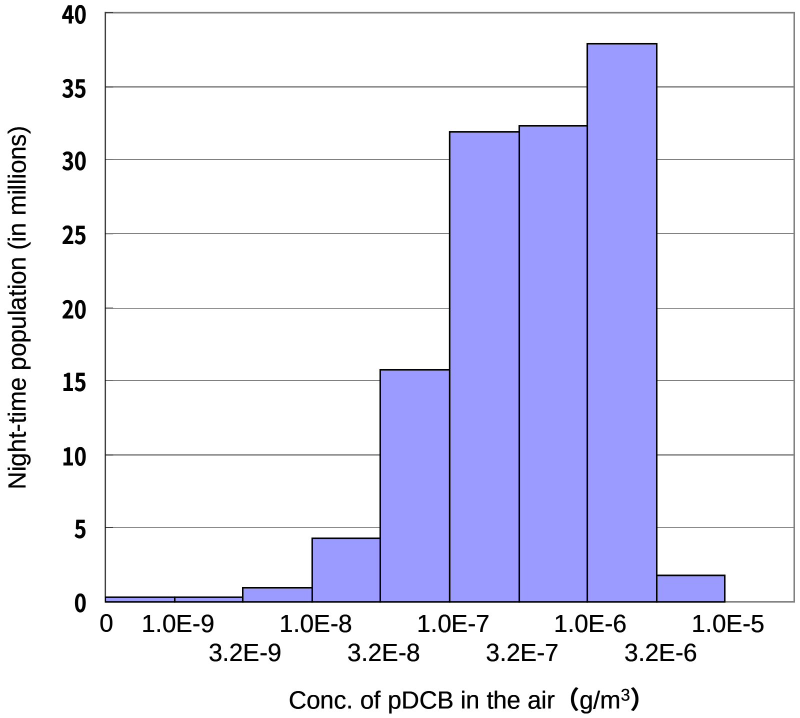

Figure 2. The histogram of conentration of pDCB in the ambient air estimated by AIST-ADMER and the numbers of people exposed to each concentration level. Frequency distributions of average concentration are the averages per 5-km mesh, weighted by night-time population per mesh, throughout Japan. The median and the arithmetic mean were 0.42 and 0.79 μg/m^3, respectively.

6. Exposure Assessment and Risk Assessment

Human exposure to pDCB was evaluated on the basis of indoor concentrations and outdoor concentrations, taking into consideration the time spent in each situation. The exposed population was divided into two groups according to their patterns of life spent. One group consisted of housewives, babies and preschool children, and elderly persons (abbreviated LT, see Table 3); the other group consisted of working people and students (ST). The exposed population was also divided into three groups depending on the amount of pDCB used in the household. These groups were “households with higher indoor usage” (H), “households with lower indoor usage” (L), and “households with no indoor usage” (N). As a result, the population as a whole was classified into a total of six groups, i.e. LT & H, LT & L, LT & N, ST & H, ST & L, and ST & N. Furthermore, the GSDs which were contributed by indoor emission sources, as obtained for the three household groups (in Chapter IV), were replaced by the corresponding GSDs for expressing distributions of yearly averages (Table 4). By using this distribution together with the outdoor concentrations obtained in Chapter V, inhalation exposure levels were estimated for the above six groups, and rates of exposure exceeding the reference concentration were identified. The reference concentration was determined to be 800 $\mu g/m^3$; this value was obtained from the value of the NOAEL (80 mg/m^3) divided by an uncertainty factor (100): the NOAEL was determined from a chronic (2-year) inhalation exposure study in mice, with the endpoint of non-neoplastic hepatic changes, and its validity was confirmed by the hazard-identification assessment in Chapter II of this document.

The proportion of the population for which the exposure concentration exceeded the reference value of 800 $\mu g/m^3$ was 5.4% for the group with the highest exposure (the group LT & H, Table 5). The ratio for the population as a whole was calculated to be 2.4%, half of which belonged to the group LT & H; the other half belonged to the group ST & H (Table 6). People in these groups need to take some measures to reduce their exposure to indoor concentrations of pDCB.

The reference point at which some actions for reducing their exposure need to be taken is presented in Figure 3, based on the one-box-model result dealt with in Chapter IV. For example, in an apartment with 70 m^2 of floor space, if the manufacturer-recommended quantity of pDCB-based moth repellent is used in 300-L drawers, the air changes per hour (ACH) throughout the year should be at least 0.5 times per hour.

Table 4. The indoor concentrations (GM) and GSD contributed by indoor sources of emission in each exposure group (averaged value throughout the household)

Type of pDCB usage in rooms (ratio to the whole) / Patterns of time spent		Households with higher indoor usage (H) (0.55)	Households with lower indoor usage (L) (0.35)	Households with no indoor usage (N) (0.10)
People spending at home long time (LT) 1)	GM ($\mu g/m^3$)	83.8	2.6	0
	GSD 3)	4.21	2.39	-
People spending at home short time (ST) 2)	GM ($\mu g/m^3$)	94.6	3.3	0
	GSD 3)	4.27	2.45	-

1) Housewives, babies, preschool children, elderly persons, and so on.
2) Working persons and students, and so on.
3) Values for distribution of yearly averages

Table 5. Frequencies by which the exposure concentration exceeds the reference concentration of 800 $\mu g/m^3$ (the ambient air concentration level: 0.42 $\mu g/m^3$) in the exposure groups.

	Households with higher indoor usage (H)	Households with lower indoor usage (L)	Households with no indoor usage (N)

People spending at home long time (LT) [1]	5.42%	0.00%	0.00%
People spending at home short time (ST) [2]	3.67%	0.00%	0.00%

[1] Housewives, babies, preschool children, elderly persons, and so on.
[2] Working persons and students, and so on.

Table 6. Types of indoor use in which individuals are subjected to an exposure concentration exceeding the reference concentration of 800 μg/m^3, and patterns of time spent indoors (when the outdoor concentration level is 0.42 μg/m^3)

	Households with higher indoor usage (H)	Households with lower indoor usage (L)	Households with no indoor usage (N)
People spending at home long time (LT)	53.7%	0.00%	0.00%
People spending at home short time (ST)	46.3%	0.00%	0.00%

*The proportion of individuals whose exposure level exceeded the reference value of 800 μg/m^3 was 2.4% to the whole population.

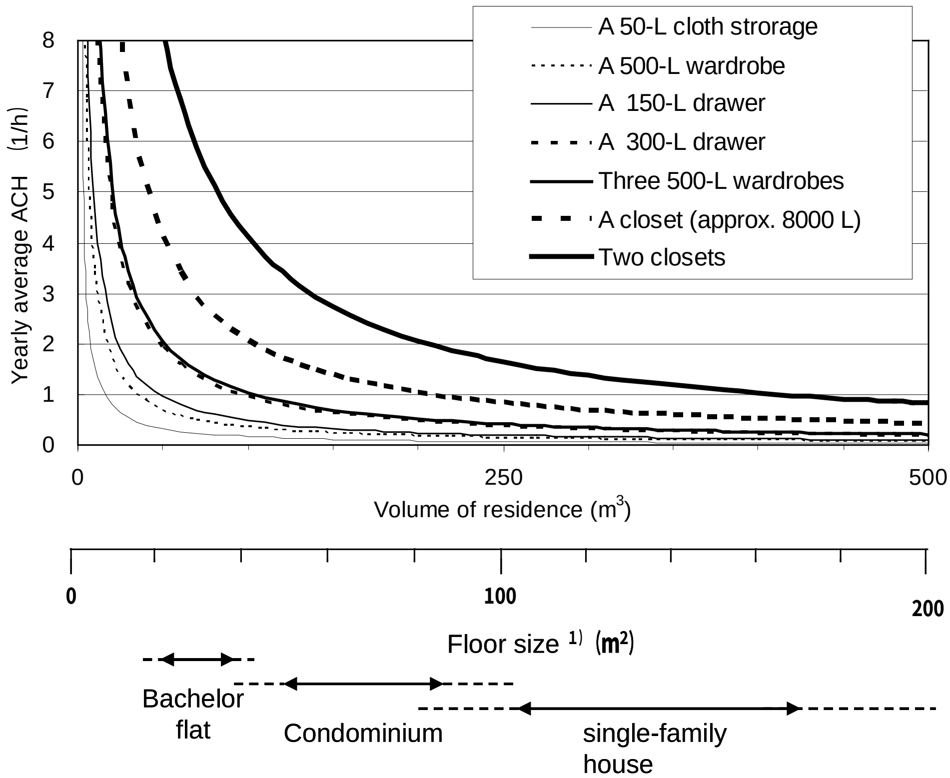

Figure 3. The relationship between the required ACH necessary to control the concentration below the reference concentration 800 μg/m^3 and the volume of the house when clothing storage units using pDCB-based moth repellent are present. (The yearly average indoor concentration of pDCB exceeds 800 μg/m^3 in the condition of below these lines).
[1] The floor size was calculated from the house volume by assuming that the height of the ceiling is 2.5 m. Also, particular housing forms in Japan are noted for reference.