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HUMAN REACTIONS TO LOW CONCENTRATIONS OF VOLATILE ORGANIC COMPOUNDS

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A group of 62 human subjects were exposed for 2.75 h to a mixture of 22 volatile organic compounds known to be indoor air pollutants. Three total concentrations of 0, 5, and 25 mg/m^3 of the same 22 compounds were used. The subjects were all healthy and without asthma, allergy, or chronic bronchitis but claimed often to suffer from dry mucous membranes in eyes, nose, or upper airways. By using a questionnaire on 26 different air quality aspects, a significant effect of exposure was found for questions related to general air quality, odour, ability to concentrate, and/or mucous membrane irritation. Continuous evaluation of irritation in eyes, nose, and throat showed significant correlation to exposure both at 5 and 25 mg/m^3. The effect was acute and showed no signs of adaptation. A digit span performance test showed decreased scores during exposure.

Introduction

The number of complaints about indoor air quality and climate has increased during the last decades. In the same period, building traditions and ventilation standards have been changed in such a way that the concentration of the indoor air pollutants may have increased in the indoor nonindustrial environment. The number and character of complaints led to the definition of the "sick building syndrome" (WHO, 1982). This syndrome (see Table 1) includes different symptoms like irritation of mucous membranes, weak neurological symptoms, and unspecific hypersensitivity reactions. These symptoms may have different causes both related to indoor climate and to the individual sufferer. Irritation of eyes, nose, and throat are among the most frequent complaints, and are similar to the effect of small concentrations of irritating organic gases and vapours from solvents. Such volatile compounds are known from the indoor climate (Mølhave and Møller, 1979; Johansson, 1982). They normally originate from building materials, and a working hypothesis was developed that these gases and vapours may be an important factor for the occurrence of symptoms such as mucous membrane irritation in the indoor environment.

The present paper describes an investigation of this hypothesis, where 62 subjects under controlled laboratory conditions were exposed to low concentrations of normally occurring indoor air pollutants, i.e., organic gases and vapours.

METHODS

The subjects

The main purpose of the experiment was to examine whether irritation symptoms were reported to subjects who were exposed to volatile organic compounds. The 62 subjects were selected among 287 persons suffering from typical indoor climate symptoms, but preliminary medical examinations showed neither somatic nor psychiatric diseases (see Fig. 1). At the start, 149 were excluded because they did not want to participate or were obviously unable (i.e., in a preliminary, short questionnaire, the subject described severe illness) to join the experiment. The remaining 138 subjects took part in the preliminary investigations. Of these, 49 subjects who did not fulfil the inclusion criteria in Table 2 were excluded. It was further ensured that only persons with no obvious medical reason for their complaints, and especially without bronchitis or asthma, joined the experiment. Then 62 subjects from this group of 80 subjects were

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Table 1. The sick building syndrome (WHO, 1982).

Irritation of eye, nose, and throat.
Dry mucous membranes and skin.
Erythema.
Mental fatigue, headache.
Airway infections, cough.
Hoarseness of voice, wheezing.
Unspecific hyperreactivity reactions.
Nausea, dizziness.

Table 2. Selection criteria.

Unspecific symptoms as given in Table 1.
Age 64–18 yr.
No signs of allergy.
No signs of asthma, chronic bronchitis, tuberculosis or chronic lung diseases.
No signs of heart diseases.
No signs of skin diseases (e.g., psoriasis).
No signs of eye diseases (e.g., glaucoma).
No chronic upper airway diseases (e.g., pharyngitis).
No psycosis or severe neurosis.
No other illnesses like cancer, diabetes, uremia, etc.
No alcohol or drug addiction.

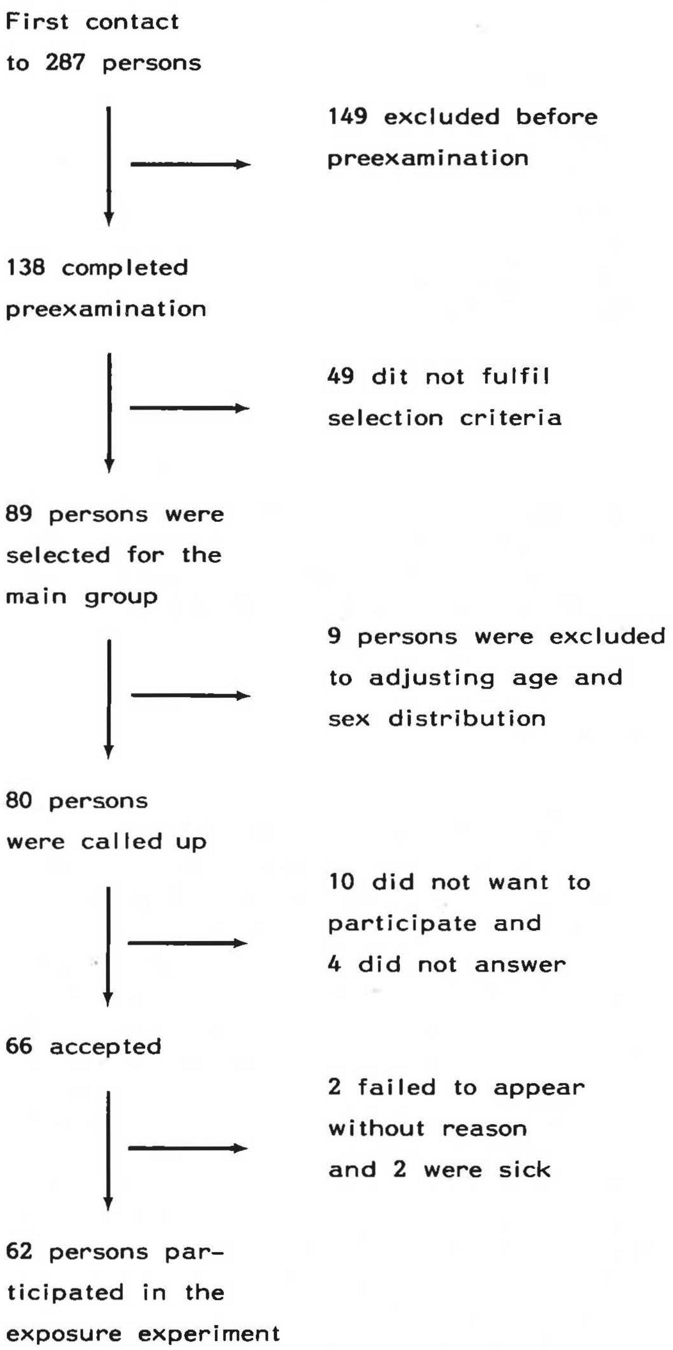


Fig. 1. The selection of 62 subjects from 287 persons.

finally selected for the exposures. Their average age was 38 yr; 63% were females and 40% were smokers.

Experimental design

The exposure was arranged in a 83-m^3 stainless steel climate chamber (Andersen *et al.*, 1983) at the Institute of Hygiene, Aarhus. The subjects were exposed to a mixture of 22 organic gases and vapours of the solvent type (Table 3). These compounds were all known as common indoor air pollutants (Mølhave and Møller, 1979; Mølhave, 1982a), and they were known or suspected mucous membrane irritants (Mølhave, 1982a; Nielsen and Alarie, 1982). The selection of the 22 compounds is further described in the Danish project report (Mølhave *et al.*, 1985). Initially, only compounds previously found in the indoor nonindustrial atmospheric environment were used. None of the compounds were carcinogens and all were known or suspected irritants. The compounds were flash evapo-

Table 3. The 22 compounds used for the exposure and their concentration ratios.

Compound	Ratio
n-Hexane	1
n-Nonane	1
n-Decane	1
n-Undecane	0.1
1-Octane	0.01
1-Decene	1
Cyclohexane	0.1
3-Xylene	10
Ethylbenzene	1
1,2,4-Trimethylbenzene	0.1
n-Propylbenzene	0.1
α-Pinene	1
n-Pentanal	0.1
n-Hexanal	1
Iso-propanol	0.1
n-Butanol	1
2-Butanone	0.1
3-Methyl-3-butanone	0.1
4-Methyl-2-pentanone	0.1
n-Butylacetat	10
Ethoxyethylacetate	1
1,2-Dichlorethane	1

Table 4. Exposure levels (mg/m³) as measured by flame ionisation detector in toluene equivalents and by charcoal techniques in absolute values.

Intended	FID ± St. Dev.	Absolute
0	0.0 ±0	0.44 ±0.3
5	4.8 ±0.3	7.39 ±1.1
25	25.4 ±1.8	32.98 ±3.3

rated at about 200 °C into the ventilation system from a mixture of all 22 substances. The composition of this mixture, therefore, reflects the concentration ratios in the chamber. The 22 compounds were all present at the same time, and their relative concentrations were constant (see Table 3). Only the total concentration varied. Three exposure concentrations were used, they were 0, 5, and 25 mg/m³ when measured as equivalent toluene concentration with flame ionisation detector (FID). These concentrations were selected to represent clean air, average concentration in new houses, and the highest concentration measured in new Danish houses (Mølhave and Møller, 1979). After the experiment the average concentrations (Table 4) were found to be 0 mg/m³, 4.8 mg/m³ (SD: 0.3), and 25.4 mg/m³ (SD: 1.8) (toluene equivalent), which were not statistically different from the intended values. These were then used in the statistical analyses. Individual concentrations of each compound were measured with charcoal sampling tubes exposed during the experiment (Mølhave, 1982b). The absolute total concentrations were found to be 0.44 mg/m³ (SD: 0.38), 7.4 mg/m³ (SD: 1.1) and 33.0 mg/m³ (SD: 3.4), which means that the actual total concentrations were slightly greater than intended.

All other exposure parameters than the total concentration were kept constant at the levels shown in Table 5. They were: temperature 23 °C (SD: 0.39), air humidity 23.3% RH (SD: 3.0), globe temperature 23.5 °C (SD: 0.3), CO_2 concentration below 0.04%, air velocity 5.5 cm per sec (SD: 5.0), light intensity 367 lux (SD: 95), sound level 59.1 LEQ-dB(A) (SD: 0.8), ventilation 9.8 air changes per hour (SD: 0.9). The workload was about 75 W, and the standard dress had an insolation value of about 0.75 clo.

Table 5. Stable exposure parameters: Intended and obtained values.

	Intended	Obtained
Air temperature (°C)	23.0 ±0.2	23.0 ±0.4[a]
Globe temperature (°C)	23.0 ±1.0	23.5 ±0.28[a]
Air humidity (%RH)	20.0 ±3	23.3 ±3.0[a]
Ventilation (800 m³/h)	10 ACH	9.8 ±0.87[b]
Air velocity (cm/sec)	10	5.5 ±5.0[b]
Sound (dB(A))	56	59.1 ±0.8[b]
Light (Lux)	250–600	367.0 ±0.8[b]
Dress (CLO)	0.75	0.75[b]
Activity (W)	75	75[b]
CO_2 (%)	0.03	<0.04[b]
Dust ((µg/m³)	<10	–

[a]No significant variation between the four exposure groups.
[b]No test/measurement.

Table 6. The four types of exposures (mg/m³) and the Latin Square design for the four weekly exposure days in four weeks.

A. Exposure Groups:	Morning Exposure	Afternoon Exposure
A	0	25
B	25	0
C	0	5
D	5	0

B. Latin square design:		Exposure Day 1 (Tue)	2 (Wed)	3 (Thu)	4 (Fri)
Week	I	A	B	C	D
	II	B	A	D	C
	III	C	D	A	B
	IV	D	C	B	A

The subjects were exposed in groups of four, and each subject was exposed only for 1 day. The exposure of four subjects in the chamber each day included two periods of 2.75 h duration, each subject thus being his own control. One of the two periods had zero concentration, the other either 5 or 25 mg/m³. The exposure was arranged in a Latin square design (Cochran and Cox, 1957) covering 16 exposure days with 4 days per week (see Table 6). The design balanced out the difference between weekdays and between morning and afternoon exposures. The exposure was double blind, and neither the subjects nor the staff knew the dosage given.

Measurements of human reactions

The measurements included both objective measurements and subjective indications. Measurements during the exposure were supplemented with measurements after the exposure to indicate if an effect continued after the last exposure (aftereffect).

To investigate if any subgroup of subjects reacted more strongly than the rest, a number of measurements were performed during the preliminary medical examination of persons for the four exposure groups in order to characterize these subjects (e.g., airway reactivity to cold air, skin sensitivity, eye and hair color etc.). Their reaction to cold air has been described elsewhere (Pedersen *et al.*, 1985).

The measurements during exposure included measurements of comfort by the use of a standardised, personal administered questionnaire including 28 questions related to indoor air quality. Six questions concerned the constant exposure parameters such as sound level, air temperature, etc. They were thus control questions. The questionnaire was used twice by each subject during control conditions and once during each of the two exposure periods. Answers were given both as an intensity estimate on a 60-mm linear scale and as the acceptability (yes or no) of the conditions addressed by each question. Odour intensity was evaluated through the ease with which the subjects could describe the odour in a questionnaire containing 44 odour-describing words (Harper test, Dravnieks and Prokop, 1983). A similar Hedonic evaluation (Dravnieks and Prokop, 1982) in terms of acceptable, neutral, or unacceptable odour were obtained by reference to a previous characterization of the 44 odour-describing words established by each subject. The odour evaluation questionnaires were attached to each of the comfort questionnaires.

The feeling of dry mucous membranes in eyes, nose, and throat were indicated by adjustments every 30 min on a linear potentiometer with a 60-mm free movement between "no complaints" and "unacceptable strong irritation." For each person the results during each exposure period were recorded as the average reading for the first 30 min (increasing concentration), for the period 30 – 165 min (constant concentration), and for the period 135 – 165 min (maximal dose). Further the reading at time zero (start) and 165 min were recorded. The eye blinking frequency was measured according to the Weber-Tschopp method (Weber-Tschopp *et al.,* 1977) using 3 min of video recording. In the recording period the subjects performed a dummy performance test. The results will be reported elsewhere.

Two performance tests were performed during the exposures. The digit span test (Wechsler, 1955) is a subtest in the Wechsler Adult Intelligence Scale (WAIS). The test is known to be sensitive to memory impairment in persons, exposed to neurotoxins. The test was used to measure short-time memory and ability to concentrate. In the test, increasing numbers of digits are verbally presented to the subject, who was to repeat the digits immediately. In the first subtest, "digit forwards," the series are repeated in the order they were presented, in the second subtest, "digit backwards," they are to be repeated in reverse order. The test is scored as the sum of the number of digits in the longest series in the two subtests repeated without errors. Each subject was tested twice a day during the last 60 min of each of the two daily exposure periods to either clean air or pollutants.

The other performance test was the graphic continuous performance test (Andersen, 1978). This test measures the ability to attend and to concentrate. It may be used as a psychomotor test as well. During the test three different patterns of simple curved lines were shown one by one to the subject. After training the patterns, the subjects had to draw five lines of each pattern from memory. To prevent the help of sight the patterns were drawn with a pencil without lead. The drawing were recorded on a copy made by carbon paper beneath the test paper. The subjects themselves were thus unable to check the results. The test was performed twice during each exposure period. The total number of errors in the three patterns and the total time used to cover three lines were recorded. Change in colour vision both concerning colour intensity and colour quality was measured by use of a previous developed test (Bælum *et al.*, 1982).

Measurements after the last of the two exposure periods were used to indicate any aftereffect. These measurements included odour threshold for *n*-butanole as measured by the triangle Olfactometer (Dravnieks and Prokop, 1975). The concentrations of sodium ($Na+$) and potassium ($K+$) were measured in tears and in nose liquids, as were the albumin concentration in tear liquids. These tests will be reported later. Furthermore, a medical examination was performed in order to exclude subjects suffering from acute upper airway infections on the exposure day, and a number of measurements were performed on each subject before or after the exposure to enable a correlation test between personal characteristics and responses during exposure. These included reactions to application of lactic acid to the check (Stingers test) and in the nose cavity (nasal spray test).

In Stingers test, a solution of 6.5% lactic acid in 0.9% sodium chloride was applied to one cheek and a sodium chloride solution to the other. The solutions were applied with cotton buds directly on the skin. In the nasal spray test, a solution of 0.45% lactic acid was sprayed into one nostril and a 0.9% sodium chloride into the other. In both tests the subject evaluated the degree of irritation on the skin or on the nasal mucosa. Over a period of 10 min the subjects evaluated differences in the irritating sensations between the two sides. The side and the intensity of irritation were recorded on a scale from 0 to 3. Both tests were performed outside the climate chamber once a day shortly after the last exposure.

The statistical analyses

Different approaches were used for the statistical analyses of discrete and continuous variables. The discrete variables were examined for exposure effect through likelihood ratio tests and X^2-test (Planchett, 1974). In some cases the Fischer exact test (Clark, 1969) had to be used. The level of significance was chosen to be 5%.

Analyses of variance were used for the continuous variables (Armitage, 1971). The tests were based on either observed results, differences between zero and exposure results or logarithmic transformed values hereof. Parameters of interest in the analysis of variance were exposure concentration (0, 5, 25 mg/m^3) or exposure group (0–5, 0–25, 5–0, 25–0) according to

Table 7. Exposure effects recorded in a questionnaire containing 28 questions about air quality aspects. Answers were given both as intensity indicated by a mark on a 60-mm long scale and as acceptability (yes or no). The table shows only those questions where one or more significant or almost significant relations were found.[a]

QUESTION	Intensity: *F*-test Analyses of Variance	Intensity: *T*-test 0/5	Intensity: *T*-test 0/25	Acceptability: Analyses of Variance
8. Air quality	+	–	+	+
9. Odour intensity	+	+	+	+
12. Skin temperature/face	–	+	–	•
15. Throat irritation	–	–	–	(+)
17. Nose irritation	–	–	–	(+)
18. Dry nose	–	–	–	(+)
19. Skin temperature/body	+	+	–	–
24. Ability to concentrate	(+)	–	+	•
27. Air quality acceptable for home	•	•	•	+
28. Would ventilate in home	•	•	•	+

[a]• = no test; + = P ≤5%; – = P ≥10%; (+) = 5 ≤*P* ≤ 10%.

exposure concentrations in the morning and afternoon period (see Table 4A). Sex, age, smoking habits, and time of the day for the exposure were used as explaining variable. The analysis were performed by the use of a standard program (Genstat, 1977).

Results

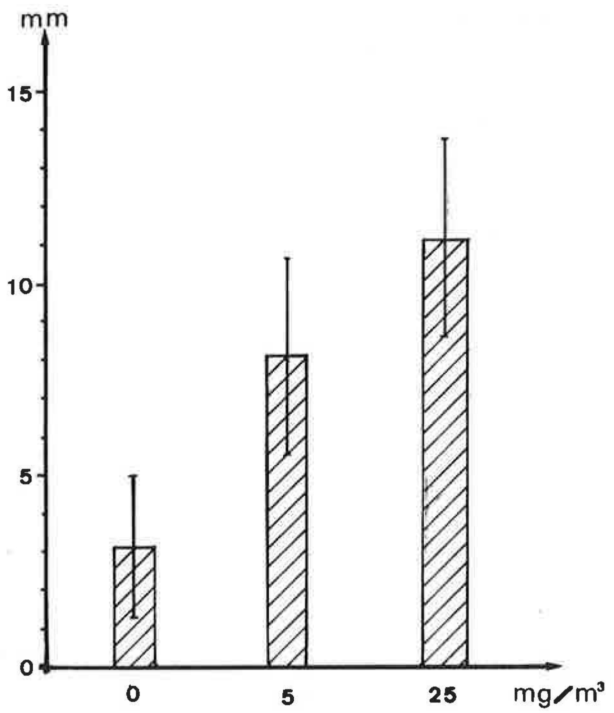
A number of significant subjective reactions to both 5 and to 25 mg/m^3 were recorded in the standardized questionnaire. These reactions are summarized in Table 7 which contains those questions where one or more significant effects were seen. An *F*-test and analysis of variance of the intensities marked on linear scale showed significant difference between exposed (5 and 25 mg/m^3) and nonexposed with regard to questions about air quality (no. 8), odour intensity (no. 9) and skin temperature (no. 19). The effect on odour intensity and air quality was significant both in the two direct questions (no. 8 and 9) and in the two control questions (no. 27 and 28). When the two exposures 5 and 25 mg/m^3 were *t*-tested separately only unacceptability of odour intensity showed significant effect of both concentrations.

Except for eye irritation, all questions with direct relation to mucous membranes irritation or air quality including the two control questions showed one or several significant or almost significant relations to exposure. Beside these, only "skin temperature" and "ability to concentrate" showed such relations. Control questions related to constant climate factors like temperature etc. showed no effect of exposure. Figures 2A and 2B show the dose-effect relationship, the linear ratings in question no. 8 (air quality) and no. 9 (odour intensity). The ordinate is difference between ratings in clean air immediately before and during the exposure to 0, 5, or 25 mg/m^3.

The degree of mucous membrane irritation was recorded regularly on the linear potentiometer. The average value for the whole exposure period was significantly correlated to the exposure level. Figure 3 shows the change with exposure of the difference between the initial setting and the average for the exposure period. A significant effect of exposure was found both at 5 and 25 mg/m^3. The mucous membrane irritation was significantly correlated to questionnaire ratings of air quality (no. 8), eye irritation (no. 10), nose irritation (no. 17), but not to odour intensity (no. 9). The subjects, therefore, seem to be able to separate air quality from odour intensity.

The change in potentiometer setting during the exposure to clean air, 5 and 25 mg/m^3 is shown in Fig. 4. During the first 30 min when the intended exposure level was reached, there was a steep increase in the effect but after this no significant further increase was observed. No clear signs of neither a threshold nor adaptation were seen during the 165 min exposure period.

No effect was seen in the eye blinking frequency despite the reported increases in eye irritation. This



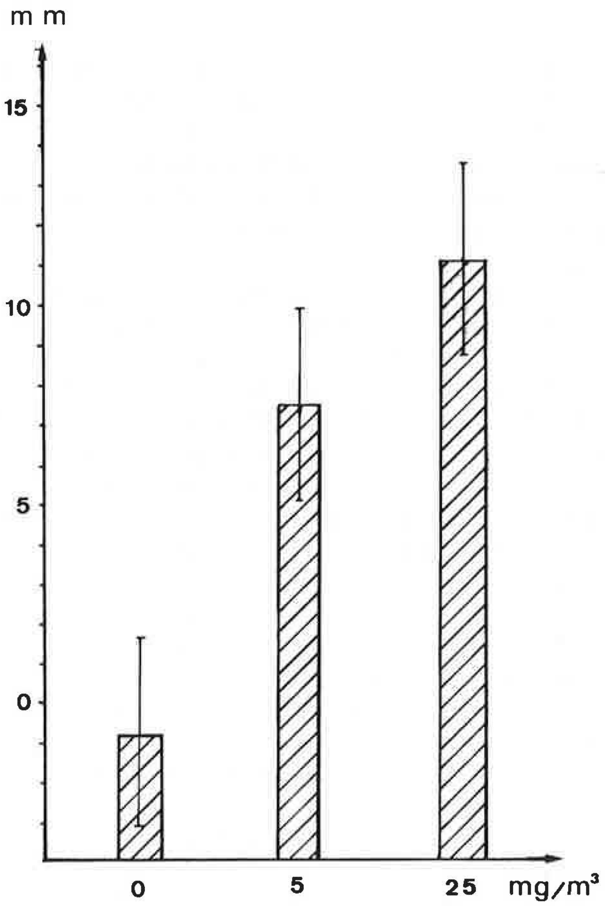


Fig. 2. Questionnaire: The dose-effect relation between concentration (mg/m³) and intensity evaluation of (A) air quality and (B) odour intensity. The ordinate is difference between exposed and unexposed condition.

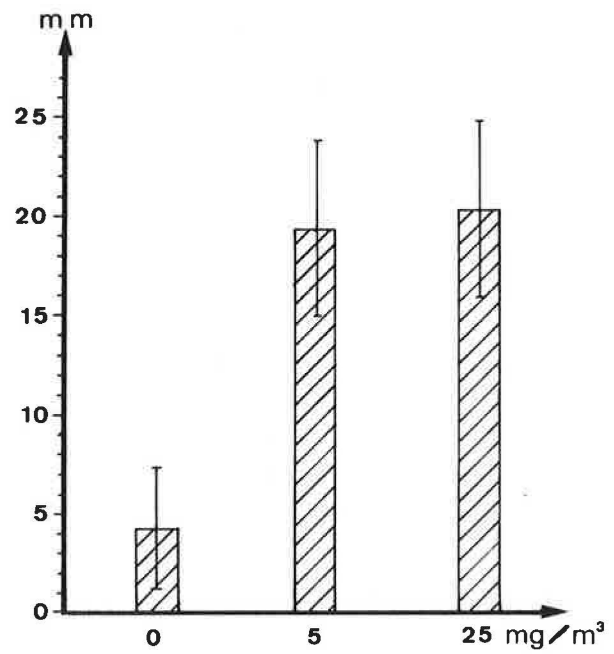


Fig. 3. Linear potentiometer: The dose-effect relation between concentration (mg/m³) and intensity evaluation of the feeling of dry mucous membranes. The ordinate is difference between average response before and during exposure.

lack of correlation must be explained by a low sensitivity of the test due to a factor 30 variation of frequency among the subjects. This will be discussed in a paper to be published later.

Odour intensity derived by the use of odour descriptive words in the Harper test showed a significant increase at both 5 and 25 mg/m^3 as shown in Fig. 5. A

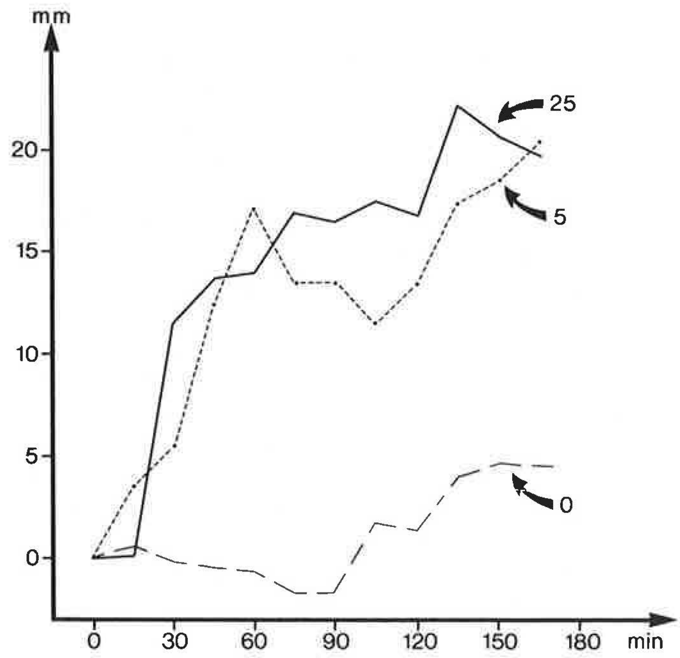


Fig. 4. Linear potentiometer: The variation in potentiometer setting during each of the three exposures. The ordinate is the difference between initial and actual setting.

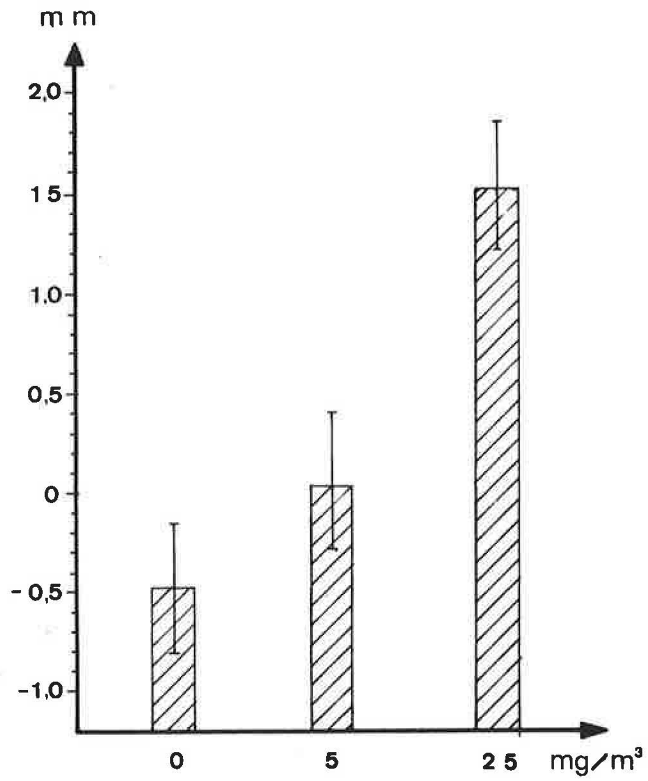


Fig. 5. The variation with exposure (mg/m³) of odour intensity as estimated from the ease with which 44 odour descriptive words were found adequate by the subjects. The ordinate is the difference in a square root transformed odour intensity index before and during exposure.

similar figure was found for odour acceptability. The analysis of variance showed no effect of time, age, sex, and smoking habits. No correlation was found between these two measures and neither odour threshold (Triangle) or potentiometer rating of mucous membrane irritation.

In the digit span tests, difference between scores during exposure and during clean air were analysed. The results are shown in Table 8. The subjects were pooled in two groups (exposed and nonexposed), with each subject being his or her own control. The analysis, therefore, looked for exposure effects and not for dose effects.

The scores in both "digit forwards" and "digit backwards" showed significant exposure effect (X^2 tests on score differences). The scores decreases significantly during exposure ($P \leq 1\%$).

The statistical analysis of the results from the graphic continuous performance test showed a wide variation in scores. An increase in scores with increasing age but no dosage or exposure effects were found. The subjective reaction to application of 6.5% lactic acid on the cheek (Stingers test) showed no significant hangover effect, although a tendency was seen (P = 10%). No effect was seen in the similar test for the nose (nasal spray test). No subgroup of hyperreactive subjects could be identified.

Discussion

Mucous membrane irritation, dryness of nose, eyes, etc., are among the most frequent complaints from the indoor environment (WHO, 1982). These acute symptoms are similar to those reported by humans exposed to irritating gases and vapours. The aim of our study was, therefore, to investigate whether a relation really exists and to demonstrate if a dose-effect relation can be established.

Mucous membrane irritation is not a well defined effect but involves sensations through several sensory systems. The mechanisms may be multifactorial as suggested by Mølhave (1985). In this experiment the physical work load was too low to influence the responses. On the other hand, mental loads such as stress and fatigue may have contributed to the fact that the significant observations were generally less significant during morning exposures than during afternoon exposures when the subjects may have become more accustomed both to the unfamiliar environment and to the different tests. A mass psychogenic bias (Colligan, 1981) was not expected, since the subjects were not allowed to discuss the experiment during the exposure and because the experiment was double blind. Furthermore, the experiment was performed according to a Latin square design that cancels out influences not related to the pure effect of exposures.

The exposure concentrations and durations corresponded to a daily dose (concentration × time) of 69 and 14 mgh/m³, respectively. The same daily doses are obtained in homes with concentrations of 3 and 0.3 mg/m³ corresponding to those found in old houses in Denmark (Mølhave and Møller, 1979). The 22 compounds used were chemically pure and handled in a way to minimize the possibility of chemical reactions. Gaschromatographic tests showed less than 1% impurities. Subsequent analysis after the experiment of charcoal samples taken during each exposure period showed that the true total concentrations were 0.44, 7.39, and 33.0 mg/m³, as indicated in Table 3.

A small amount of toluene occurred as a constant background contaminant due to the daily cleaning procedure. Toluene is, however, a weak irritant (Nielsen

Table 8. The number of subjects with total scores in the digit span test higher or lower than the average. The subjects have been arranged according to morning or afternoon exposure (5 or 25 mg/m³).

Number of Subjects with Score Difference	Morning (5–0, 25–0)	Afternoon (0.5, 0–25)
<0	2	15
>0	22	9

and Alarie, 1982) and the contamination was considered irrelevant for the interpretation of the experiment. Table 4 shows further that a true "clean air" exposure was not obtained. This contamination was due to offgassing of pollutants absorbed to the walls, etc., during the previous exposure period. Most of the statistical analyses were based on differences between "clean air" exposures and exposures to the 22 compounds. The true magnitude of the effects may have been underestimated in the case that the contaminating 0.4 mg/m^3 has any biological effect at all.

The subjects were not selected randomly from the whole Danish population but from medical clinics, research institutes etc. to whom they had reported discomfort which they attribute to the indoor climate. Only subjects for whom no obvious medical disease (e.g. asthma or allergy), environmental (e.g. high air temperature etc.) or other cause could be found for their discomfort were used in the experiment. As a group they may be considered more healthy than the general population as all sick or debilitated subjects were excluded. The statistical analyses showed that the subjects were unable to identify any variation in the intended stable exposure parameters shown in Table 5.

In conclusion, the controlled and balanced exposure experiment has shown that a group of healthy persons reacted (see Figs. 2–4) acutely in their subjective intensity evaluations of air quality, odour intensity and feeling of dry mucous membranes to both 5 and 25 mg/m^3 of a mixture of organic gases and vapours known as typical air pollutants from the nonindustrial indoor environment. These acute complaints or symptoms were not provoked by the odour intensity, and they showed no signs of adaptation during exposure for 2.75 h. In the answers to a number of questions dealing with indoor air quality, the subjects reacted more to 5 and to 25 mg/m^3 than to clean air. The reports on feelings of dry mucous membranes were strongly correlated with exposure, and correlated further with the questionnaire reports of irritation symptoms and deteriorated air quality, but not to reports of odour intensity. The subjective evaluations about odour intensity and odour quality, therefore, seem to refer to different aspects of indoor air quality. The change over time of the average intensity evaluation of sensation of dry mucous membranes during exposure to 0, 5, or 25 mg/m^3 showed an immediate effect within 30 min. There were no signs of adaptation. Odour intensity during exposure as estimated by use of a separate questionnaire was correlated to exposure. Increased exposure was also associated with a significant decrease in odour threshold as measured with the triangle method. A standard digit span test showed a decreased memory for digits both during exposure to 5 and to 25 mg/m^3.

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