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Suprathreshold intensity and annoyance reactions in experimental challenge to toluene and n-butyl acetate among subjects with long-term solvent exposure

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Objectives This study explores reactions to low-level chemical challenge, aiming at the development of test procedures for assessing individual sensitivity to smells and chemicals.

Methods Subjects with symptoms and neuropsychological test results compatible with toxic encephalopathy type 2A (TE-2A) and 2B (TE-2B) and unexposed referents (N=12 in each group) were challenged in an exposure chamber. Toluene exposure was started at 11 mg/m^3, and it followed a geometric progression scale with a ratio of 2, until reaching 180 mg/m^3. In a counterbalanced design, the subjects were similarly exposed to n-butyl acetate starting at a concentration of 14 mg/m^3 and increasing to 228 mg/m^3. At each exposure level, smell intensity was measured on a 7-step category scale. Mucous membrane irritation and annoyance reactions were rated on visual analogue scales.

Results Both TE groups showed high sensitivity to the low-level solvent challenge, which provoked immediate annoyance and fatigue reactions. In particular the TE-2B group related smell intensity to various annoyance dimensions during exposure to n-butyl acetate, a pattern not observed during toluene exposure. The reference group clearly separated smell intensity and annoyance reactions in both exposure conditions.

Conclusions The reaction of the TE cases suggests that chemical sensitivity can be distinguished from normal annoyance reactions by the inability to differentiate between smell intensity and an experience of irritation from mucous membranes in air concentrations well below the trigeminal irritation threshold level. Fatigue coreactivity in challenges to single substances below the neurotoxic level may also be important.

Key terms cacosmia, chemical sensitivity, exposure chamber, toxic encephalopathy.

Annoyance and sickness reactions to chemicals in low ambient-air concentrations, with or without smell perception, have been described for different settings. One is reaction to indoor climate, which is basically related to problems in the physical environment (1). Another is the reaction of feeling physically sick, elicited by common smells (2). A greater problem is the multiple chemical sensitivity syndrome that has initiated intense debate and research efforts in North America (3). Well-known in occupational medicine is the development of solvent sensitivity after long-term exposure to mixtures of solvents (4, 5). Subjects complaining of chemical sensitivity present multiple and nonspecific symptoms, and these complaints have led to a variety of hypotheses on mechanisms and models for clinical evaluation (6—9).

In various environmental syndromes with unknown etiology there seems to be an overlapping of symptoms (10, 11). Thus the causal attribution preferred by patient or physician cannot be suggested as a suitable diagnosis without any specific criteria. In some circumstances it may be useful to test whether a specific hypersensitivity is a physiological or learned response (12).

We are of the opinion that a standardized procedure with predetermined chemical substances should be used to evaluate generalized chemical sensitivity. The goal should be to determine whether sensitivity can be objectively established and whether physiological or psychological pathways, or both, lead to the symptoms. In chemically sensitive subjects an objective experimental exposure level of zero does not necessarily correspond with

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that of being subjectively unexposed. Therefore such a challenge would inherently deviate in design and evaluation from established methods for measuring olfactory function (eg, magnitude estimations known to follow a power function) (13). To avoid triggering strong immediate responses, the reference level has to be the phase of objective zero exposure to the test substance.

The present investigation is part of a research program aiming at the development of procedures for assessing individual sensitivity to chemicals and differentiating the reactions from neurotoxic injury. So that a model for evaluating chemically sensitive subjects could be established, patients with toxic encephalopathy after long-term occupational exposure to solvents, and an unexposed reference group, were challenged with the solvents n-butyl acetate (BuAc) and toluene. The air concentrations used were below previously reported thresholds for acute neurotoxic effects and, most importantly, well below thresholds for trigeminal irritation, reported to be 475—959 mg/m^3 for BuAc and 750—1125 mg/m^3 for toluene (14—16).

The specific aim was to determine whether subjects with solvent-induced symptoms had an increase in various dimensions of suprathreshold sensitivity to low air concentrations of solvents.

Subjects and methods

Subjects

All the subjects were men in the age range of 28 to 66 years with toxic encephalopathy (TE) type 2A or type 2B and unexposed referents. Each group comprised 12 subjects. They have previously been described in detail with electrophysiological and some neuropsychological findings and exposure history (17, unpublished report by Österberg K et al). The clinical criteria for TE have followed qualitative international consensus agreements. Both the TE-2A and TE-2B subjects had mixed subjective symptoms, but only the TE-2B subjects had subnormal neuropsychological test results that suggested organic brain involvement, congruent with the criteria for the classification of TE given at the international solvent workshop in the United States in 1986 (18). TE-2B corresponds to "mild" or "severe" chronic TE according to the classification criteria of the World Health Organization (WHO) (19). TE-2A has no representation in the WHO system.

The TE-2A and TE-2B groups had been solvent-exposed during a period of 7—35 (mean 22) years and 7—44 (mean 23) years, respectively. The estimated magnitude of exposure was similar in the 2 groups (17). At the time of the present examination, 4 TE-2A and 5 TE-2B subjects occasionally had slight contact with solvents. The reference subjects had had neither past nor present solvent exposure.

Before being definitely included, all the subjects underwent a comprehensive medical work-up to confirm the absence of any other disease of importance. Furthermore, they had a health check-up on each day of the exposure challenge. No illness whatsoever, including the common cold, was allowed during the 2 weeks preceding the chamber sessions. Qualitative olfactory function was checked before each challenge with a smell test including cocoa, coffee, peppermint oil, and n-amyl acetate (smells of banana).

After each exposure session, the olfactory function was quantitatively assessed with n-butanol as the test odorant. The procedure was slightly modified from that described for the threshold test by the Connecticut Chemosensory Clinical Research Center (20).

The measurements showed that 32 of the 36 subjects were norosmic. One subject in either TE group had mild hyposmia. In the reference group, 1 subject had moderate, respectively severe hyposmia.

Experimental design

The exposure sessions were carried out in a counterbalanced repeated-measures design across groups with respect to time (morning-afternoon), substance sequence, and test leader. The subjects were informed that the exposures were below current hygienic threshold limits and were given information about the duration of the sessions. No other details of the exposure design, including the names of the substances, were given until both sessions were completed. The ethics committee of Lund University approved the study (LU 94—236), and all the participants gave their informed consent.

The exposure was performed in a chamber with a volume of 2.15 m^3 (1.03×1.03×2.03 m) with solid walls on 3 sides with a front door made of toughened glass on the 4th side. The inlet to the chamber was at floor level and the outlet was placed at the top of the chamber. The turnover rate was 96/hour, and the chamber temperature varied between 20.4 and 23.5°C.

The chamber sessions began with 20 minutes in clean air (zero phase). The exposure was then started at 3 ppm (11 mg/m^3 for toluene or 14 mg/m^3 for n-butyl acetate), and it followed a geometric progression scale with a ratio of 2 until reaching 48 ppm (180 mg/m^3 for toluene or 228 mg/m^3 for n-butyl acetate). Each step of exposure was monitored with an infrared spectrophotometer (Miran 1-A). Typically, the air concentration stabilized within 3 minutes after each increase and varied less than 10% at each exposure level.

The duration of the 7 chamber periods was 20 minutes at 0 ppm, 10 minutes at 3 ppm, 10 minutes at 6 ppm, 20 minutes at 12 ppm, 10 minutes at 24 ppm, 20 minutes

at 48 ppm, and finally 10 min at 0 ppm. Total time in the chamber was approximately 2 hours.

Challenge response

Before entering the chamber the subjects practiced the response procedures. After a short walk in fresh air they entered the chamber. During each of the 7 periods they answered 35 questions. In the three 20-minute periods they were also given tests for reaction time and perceptual speed, to be reported elsewhere. The questions were presented to the subjects on a 17-inch color video display screen, visible through the glass door. The subjects responded on a simplified keyboard inside the chamber. The administration was carried out with the programmable questionnaire module in the Automated Psychological Test System (APT) (21).

Smell intensity was measured on a 7-step category scale: none, very weak, weak, distinct, strong, very strong, extremely strong (22). Smell annoyance and irritation from nose, eyes, mouth, and throat was rated on visual analogue scales (VAS) (range 0—100). Similarly, the subjects rated drowsiness, headache, and concentration difficulties, as well as disturbance from other factors in the environment (ie, light, temperature, humidity, and sound level).

Data analysis

Data were analyzed by use of the statistical software SPSS® V7.52 for Windows®. The separate response items for eye, mouth-throat, and nose irritation were averaged to form a mucous membrane irritation index. Drowsiness, headache, and concentration difficulties were averaged to form a fatigue index. Disturbance from other factors (ie, light, temperature, humidity and sound level) was combined to constitute an environment index. To obtain a combined response measure for each subject and challenge, the individual response slopes from the zero phase through the 5 steps of geometric exposure increase were estimated with the curve fit module. The chamber periods were entered in the regression as independent variables coded as 1 to 6. The regression thus corresponded to an approximated log-linear model including the zero-phase reactions in the chamber. This regression model gave generally statistically significant individual curve fits, which did not improve with logarithmic transformation of the dependent variable.

Comparisons between groups, and between substances within groups, were made by a general linear models repeated measures analysis in a 2-factorial model, using 1 factor for group and 1 for substance sequence. For the analysis of the zero phases, only the group factor was included. In post hoc analyses between the groups, t-tests with Bonferroni correction for multiple comparisons were used. Paired t-tests were used groupwise when significant interactions with the group factor appeared in the comparisons between the 2 substances within the groups.

Results

Zero phases

Several subjects reported some intensity of smell, in particular some degree of the various annoyances already in the zero phases (0 ppm). The various ratings before exposure did not differ between either session (table 1). Between the groups there was no statistically significant difference concerning the ratings in the zero phase of the BuAc sessions. In the zero phase of the toluene sessions, the TE-2A group scored higher on smell annoyance than the 2 other groups ($P<0.05$). The TE-2A group also had higher ratings than the referents for mucous membrane irritation ($P=0.02$) and fatigue ($P=0.04$) of the zero phase in the toluene session.

Smell intensity and annoyance

For smell intensity, there was a greater slope (regression coefficient b), that is, a higher intensity increment per exposure step for BuAc than for toluene (figures 1 and 2, table 2). In addition, the within-group analysis showed statistically significant interactions with the factor group and exposure sequence. The greatest difference between the intensity slopes was found in the TE-2A group followed by the reference group ($P=0.006$ and $P<0.001$, respectively). The TE-2B subjects had high intensity slopes for both substances. The subjects challenged with the substance sequence BuAc-toluene had a mean slope difference of 0.34 between the BuAc and toluene intensity versus the 0.16 for the subjects challenged in the opposite sequence (interaction $P=0.049$).

The difference between the groups was also statistically significant. A post hoc analysis revealed higher intensity experience for the TE-2B group than for the 2 other groups during the toluene exposure ($P<0.001$). The intensity ratings for BuAc were of the same magnitude in all the groups.

For smell annoyance, all the groups had higher scores for BuAc than for toluene. Neither interaction nor the between-group difference was found to be statistically significant (figures 3 and 4, table 2).

Mucous membrane irritation

BuAc was rated as slightly more irritative than toluene in the mucous membranes (table 3). The difference, however, was not statistically significant. There was an interaction with exposure sequence ($P<0.001$). Most of the subjects (83%) exposed to BuAc in their first session experienced this substance as more irritating, and most of those starting with toluene (78%) found that to be more irritating.

Table 1. Ratings on the intensity and annoyance scales or indices during the initial zero phases without chemical exposure. (TE-2A and TE-2B = toxic encephalopathy, type 2A and type 2 B, respectively)

	Referents (N=12)		TE-2A (N=12)		TE-2B (N=12)		P-value[a]	
	Mean	SD	Mean	SD	Mean	SD	Comparison between groups	Comparison between sessions within groups
Smell intensity (steps 0—6)							0.088	0.55
Toluene	1.3	0.8	1.9	1.1	1.7	1.1		
n-Butyl acetate	1.2	0.6	1.9	1.5	1.4	0.7		
Smell annoyance (range 0—100)							0.041	0.16
Toluene	0.5	1.2	10.0[b,c]	15.5	0	0		
n-Butyl acetate	4.0	12.3	15.3	27.8	1.8	3.5		
Mucous membrane irritation (range 0—100)							0.047	0.88
Toluene	1.9	3.1	19.6[b]	21.5	9.7	14.7		
n-Butyl acetate	5.4	6.0	16.3	22.7	8.4	10.1		
Fatigue (range 0—100)							0.023	0.88
Toluene	3.4	6.8	21.6[b]	22.8	14.0	17.2		
n-Butyl acetate	2.4	4.0	18.5	24.5	16.6	20.5		
Environmental annoyance (range 0—100)							0.42	0.38
Toluene	23.1	9.4	30.0	13.4	24.1	7.7		
n-Butyl acetate	22.6	12.5	26.3	15.2	23.2	12.0		

[a] P-values in general linear models repeated measures analyses. [b] TE-2A versus referents; P<0.05 in the post hoc Bonferroni corrected t-test.
[c] TE-2A versus TE-2B; P<0.05 in the post hoc Bonferroni corrected t-test.

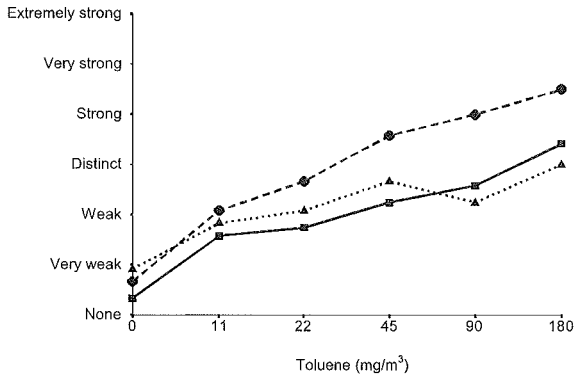

Figure 1. Ratings of toluene smell intensity (mean values) as the concentrations increased for the TE-2A (dotted line), TE -2B (dashed line), and reference (solid line) groups. (TE-2A and TE-2B = toxic encepalopathy, type 2A and type 2B, respectively)

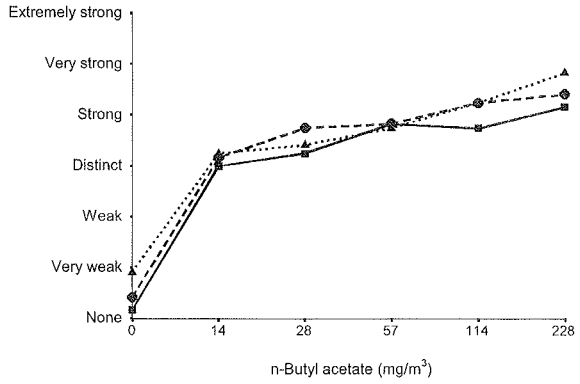

Figure 2. Ratings of n-butyl acetate smell intensity (mean values) as the concentrations increased for the TE-2A (dotted line), TE-2B (dashed line), and reference (solid line) groups.(TE-2A and TE-2B = toxic encepalopathy, type 2A and type 2B, respectively)

Table 2. Suprathreshold regression coefficients for smell intensity and smell annoyance at geometrically increasing steps of toluene and n-butyl acetate exposure in the TE-2A, TE-2B, and reference groups. (TE-2A and TE-2B = toxic encepalopathy, type 2A and type 2B, respectively)

	Referents (N=12)		TE-2A (N=12)		TE-2B (N=12)		Comparison between groups[a,b]		Comparison between substances within groups	
	Mean	SD	Mean	SD	Mean	SD	Group	Sequence	P-value	P interaction[c]
Smell intensity (steps 0—6)							0.036	0.14	<0.001	group 0.017 sequence 0.049
Toluene	0.79	0.15	0.73	0.32	1.05	0.12				
n-Butyl acetate	1.05	0.18	1.14	0.29	1.12	0.21				
Smell annoyance (range 0—100)							0.15	0.091	<0.001	
Toluene	6.8	4.6	9.6	4.1	11.0	5.8				
n-Butyl acetate	10.6	5.6	14.8	6.0	13.3	7.6				

[a] P-values in general linear models repeated measures analyses. [b] No interaction showed a P-value of <0.05.
[c] Of 3 possible interaction terms, group, substance sequence, and group×(substance sequence), only those with P<0.05 are shown.

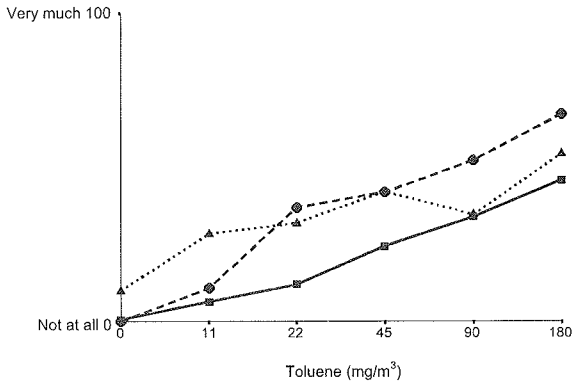

Figure 3. Smell annoyance ratings (means on the visual analogue scale) at increasing toluene concentrations for the TE-2A (dotted line), TE-2B (dashed line), and reference (solid line) groups. (TE-2A and TE-2B = toxic encepalopathy, type 2A and type 2B, respectively)

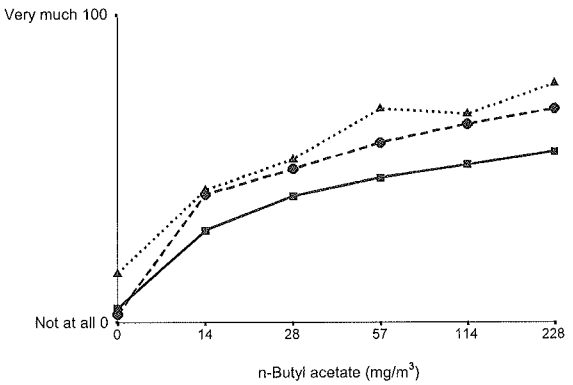

Figure 4. Smell annoyance ratings (means on the visual analogue scale) at increasing n-butyl acetate concentrations for the TE-2A (dotted line), TE-2B (dashed line) and reference (solid line) groups. (TE-2A and TE-2B = toxic encepalopathy, type 2A and type 2B, respectively)

Table 3. Suprathreshold regression coefficients of mucous membrane irritation, fatigue, and annoyance from environmental factors other than smell at geometrically increasing steps of toluene and n-butyl acetate exposure in the TE-2A, TE-2B, and reference groups. (TE-2A and TE-2B = toxic encepalopathy, type 2A and type 2B, respectively)

	Referents (N=12)		TE-2A (N=12)		TE-2B (N=12)		Comparison between groups[a,b]		Comparison between substances within groups	
	Mean	SD	Mean	SD	Mean	SD	Group	Sequence	P-value	P interaction[c]
Mucous membrane irritation							0.012	0.043	0.093	sequence <0.001
Toluene	2.1	2.4	7.8	5.0	7.8	5.5				
n-Butyl acetate	4.2	4.9	8.5	5.8	8.1	5.5				
Fatigue							<0.001	0.023	0.020	sequence 0.011
Toluene	1.0	1.5	7.8	6.1	6.8	5.7				
n-Butyl acetate	1.7	2.0	9.0	6.2	8.8	6.2				
Environmental annoyance							0.16	0.085	0.75	
Toluene	6.5	2.8	8.7	3.9	6.4	2.1				
n-Butyl acetate	6.2	3.0	8.7	4.3	7.1	3.6				

[a] P-values in general linear models repeated-measures analyses. [b] No interaction showed a P-value of <0.05.
[c] Of 3 possible interaction terms, group, substance sequence, and group×(substance sequence), only those with P<0.05 are shown.

Table 4. Exposure challenge to toluene — correlation (Pearson's r) between the regression slopes for smell intensity, and the annoyance scales or indices in the TE-2A, TE-2B, and reference groups. (TE-2A and TE-2B = toxic encepalopathy, type 2A and type 2B, respectively)

	Smell intensity	Smell annoyance	Mucous membrane irritation	Fatigue
Reference group				
Smell annoyance	0.61*	.	.	.
Mucous membrane irritation	0.08	0.19	.	.
Fatigue	−0.53	−0.14	0.41	.
Environmental annoyance	0.13	0.22	0.10	0.04
TE-2A group				
Smell annoyance	0.08	.	.	.
Mucous membrane irritation	−0.33	0.79**	.	.
Fatigue	−0.40	0.40	0.74**	.
Environmental annoyance	−0.27	0.50	0.58*	0.72**
TE-2B group				
Smell annoyance	0.50	.	.	.
Mucous membrane irritation	0.36	0.35	.	.
Fatigue	0.51	0.62*	0.38	.
Environmental annoyance	0.66*	0.75**	0.52	0.76**

* P<0.05, ** P<0.01 two-sided.

Table 5. Exposure challenge to n-butyl acetate — correlation (Pearson's r) between the regression slopes for smell intensity and the annoyance scales or indices in the TE-2A, TE-2B, and reference groups. (TE-2A and TE-2B = toxic encepalopathy, type 2A and type 2B, respectively)

	Smell intensity	Smell annoyance	Mucous membrane irritation	Fatigue
Reference group				
Smell annoyance	0.17	.	.	.
Mucous membrane irritation	0.23	0.78**	.	.
Fatigue	0.033	0.57	0.87**	.
Environmental annoyance	0.004	0.47	0.53	0.34
TE-2A group				
Smell annoyance	0.83**	.	.	.
Mucous membrane irritation	0.54	0.74**	.	.
Fatigue	0.49	0.70*	0.81**	.
Environmental annoyance	0.34	0.68*	0.87**	0.68*
TE-2B group				
Smell annoyance	0.86**	.	.	.
Mucous membrane irritation	0.76**	0.80**	.	.
Fatigue	0.75**	0.83**	0.80**	.
Environmental annoyance	0.49	0.64*	0.68*	0.88**

* P<0.05, ** P<0.01 two-sided.

The between-group, post hoc analysis showed that the TE-2A and TE-2B groups were more irritated by toluene than the referents were (P=0.009 and 0.008, respectively). The higher level of irritation in the BuAc exposure in the TE groups was not statistically significant. Subjects exposed to BuAc at the first session found this substance to be more irritating than did those starting with toluene (mean of slopes 10 versus 4, P=0.001).

Fatigue

BuAc induced higher fatigue scores than toluene (P=0.02) (table 3). There was an interaction with substance sequence (P=0.01). The subjects tended to find the substance first encountered to have the greater influence.

Comparisons between groups showed that the 2 TE groups had higher fatigue scores than the reference group when exposed to either substance (P<0.001). Those exposed to BuAc at the first session experienced more fatigue during BuAc exposure than did those starting with toluene (mean of slopes 9 versus 4, P=0.007).

Environmental annoyance

The ratings of environmental annoyance did not show any statistically significant differences between the reactions of either group during exposure to either substance (table 3). Nor did the substance sequence matter.

Correlation

The correlation matrices for the 3 groups revealed different patterns of relationship between the intensity and annoyance scores (tables 4 and 5). The referents did not relate the smell intensity to feelings of annoyance when exposed to either toluene or BuAc, with the exception of the correlation between smell intensity and smell annoyance when exposed to toluene. Both TE groups, in particular the TE-2B group, related smell intensity to the various annoyance dimensions when exposed to BuAc but not to toluene.

Another pattern shown was that the 2 TE groups showed a strong correlation between their various expressions of annoyance when exposed to either toluene or BuAc. This finding was the most distinct for the BuAc exposure, in which there was also a relationship in the reference group between smell annoyance and the other annoyance dimensions.

Discussion

As was expected, BuAc exposure produced a stronger smell intensity and led to more annoyance than toluene among both the unexposed subjects and those with long-term exposure to solvents with and without deviations in cognitive functioning. Although BuAc was a stronger irritant than toluene, the substance presented to the subjects at the first challenge tended to provoke more mucous membrane irritation and fatigue. Generally, the 2 groups of toxic encephalopathy, TE-2A and TE-2B experienced a stronger intensity of smell and greater annoyance reactions than the referents. This was particularly the case when they were exposed to toluene, while BuAc, unfortunately, already at the initial exposure level of 14 mg/m^3, was found to have a distinct to strong smell and was found unpleasant by all 3 groups. The latter aspect is illustrated by means of 30—43 on the smell annoyance VAS. As a consequence of these early reactions, the differences between the groups became smaller in BuAc exposure than in exposure to toluene. It also implies that BuAc exposure should begin at a lower air concentration (eg, 3.5 mg/m^3).

The stronger reaction to the substance first encountered might be due to the persons' expectancy of chemical-induced annoyance. Tension might be another reason for the relatively greater irritation and annoyance found in the first session, irrespective of substance. Such factors might also explain the higher annoyance and irritation ratings given by the TE-2A group in the first chamber period, which was not known by the subjects to be a true zero exposure phase. In the toluene exposure, both the reference and the 2 TE groups distinguished smell intensity from most dimensions of annoyance. In the BuAc exposure this ability was poor for the 2 TE groups, in particular for TE-2B.

Olfactory adaptation was counteracted by forcing the subjects to respond immediately after the changes in air concentration. Any bias possibly introduced by adaptation would lead to less pronounced reactivity. At a BuAc concentration of 70 mg/m^3 Iregren et al (23) found no adaptation concerning irritation during 15 minutes and only slight irritation during 4 hours. In exposure to mixtures of volatile organic compounds at a constant level, adaptation was 30% on the intensity scores after 2 hours, and the irritation score was constant during the same period (24).

Our results differ from those obtained in the study on previously unexposed subjects, in whom BuAc at 70 mg/m^3 and 700 mg/m^3 induced only slight annoyance reactions at the higher level (23). This discrepancy suggests previously experienced annoyance to be of importance for the reactions, which is in accordance with the notion of tuning the sensory system or of perceptual learning (1, 25). Our results also suggest an acquired inability in the TE groups to discriminate between basic sensory input (ie, intensity) and the emotional reactions (ie, annoyance) to this sensation. Since this observation was restricted to the BuAc challenge, neurotoxic influence is not the likely cause. Our postchallenge quantitative measurement of olfactory thresholds did not reveal

any aberration in olfactory function that could explain the reaction differences. Thus our results are in accordance with the findings of both cacosmia and normal olfactory function after long-term exposure to solvents (5, 26).

In conclusion, our results suggest that chemical sensitivity can be distinguished from normal annoyance reactions by the inability of sensitive subjects to discriminate between smell intensity and experiences of irritation and annoyance in air concentrations well below the trigeminal irritation threshold. Another important sensitivity sign might be fatigue reactions at concentrations of single substances well below neurotoxic levels. Further studies on subjects being highly sensitive to single chemicals or odors should provide some answer to our suggestions.

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