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Psychological test performance during experimental challenge to toluene and n-butyl acetate in cases of solvent-induced toxic encephalopathy

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Objectives This study determined whether performance in neurobehavioral tests deteriorates during subjectively annoying chemical challenge below known neurotoxic thresholds among persons with toxic encephalopathy with subjective hypersensitivity to chemicals.

Methods Subjects with symptoms and previous neuropsychological test results compatible with toxic encephalopathy (TE) of either type 2A (N=12) or 2B (N=12) and unexposed referents (N=12) were challenged in an exposure chamber. In a counterbalanced design, the subjects were exposed on 2 occasions to increasing air concentrations of n-butyl acetate and toluene at levels well below the thresholds for neurotoxic effects. Attention and motor speed tests were given (i) in room air outside the chamber before the challenge, (ii) in room air inside the chamber before the exposure, (iii) at 12 ppm (44 or 56 mg/m3), and (iv) at 48 ppm (180 or 228 mg/m3).

Results For both substances the TE groups showed a slight increase (deterioration) in the simple reaction-time task during chemical exposure, but not in the complex reaction-time task or in the digit symbol test of the Wechsler Adult Intelligence Scale. Contrary to reference subjects, the TE subjects did not show any improvement or learning effect in the digit symbol test over the chamber phases. n-Butyl acetate tended to affect cognitive functioning more obviously than toluene did. Suggestion or expectancy effects were not observed in any group in the clean-air baseline conditions.

Conclusions The results do not support the notion that men with subjective hypersensitivity to chemicals would be more affected than healthy men regarding cognitive functioning during annoying solvent exposure below thresholds for acute neurotoxic effects.

Key terms cacosisma, chemical sensitivity, exposure chamber, neuropsychological tests.

Feeling ill as a result of being exposed to odors of chemicals is common among patients with toxic encephalopathy (TE) after long-term solvent exposure (1). Slight annoyance reactions to various environmental odors is also frequent in the general population (2). Lately, special attention has been given to a condition of widely generalized hypersensitivity to chemicals or odors, termed multiple chemical sensitivity (3). This condition of acquired intolerance for odors may lead to a severely restricted functional capacity in everyday life. Since symptoms are nonspecific, the causal attribution preferred by patient or physician may introduce problems. If it were possible to test whether the hypersensitivity symptoms are of a physiological nature or whether they represent a learned response, or even suggestion, the diagnostic situation would be much clarified (4).

The present study is part of a research program aiming at the development of procedures for the assessment of individual sensitivity to chemicals, and also for the differentiation of various hypersensitivity reactions from reactions characteristic of neurotoxic damage in toxic encephalopathy. Such an enterprise may take its starting point by studying subjective hypersensitivity among previously heavily exposed and symptomatic workers.
whose intolerance reactions are well known within occupational medicine, yet not understood. A next step may be to compare the results with chamber challenge reactions among male and female patients without previous significant exposure causing subjective hypersensitivity, corresponding to the multiple chemical sensitivity syndrome. We have recently shown that TE subjects report higher subjective intensity and annoyance than healthy referents do when exposed to the solvents n-butyl acetate (BuAc) and toluene at air concentrations below reported thresholds for acute neurotoxic effects and trigeminal irritation (5). The present study supplements the previous observations with additional data from neuropsychological tests of sustained attention and motor or perceptual speed performed during the chamber sessions.

The specific aim was to study whether TE patients with symptoms of low-dose solvent intolerance would show an objective deterioration in neuropsychological tests when their performance was compared with the performance of healthy reference subjects, corresponding to the previously reported higher subjective annoyance levels, during solvent exposure well below thresholds for known acute neurotoxic effects.

**Subjects and methods**

The present data were collected during a chamber challenge at exposure levels well below the known threshold for acute neurotoxic effects. The intention was to induce annoyance, by using a strongly smelling but less neurotoxic substance (BuAc) and a weak-to-moderately smelling more neurotoxic substance (toluene), while studying cognitive performance on tests of attention and perceptual or motor speed.

**Subjects**

The TE cases were men aged 28 to 66 years, defined as either TE type 2A or TE type 2B according to the categories established at the Raleigh solvent workshop in the United States in 1986 (6). Both TE groups had symptoms common for the disorder, including subjective hypersensitivity to solvents and other chemical smells. The TE-2B cases differed from the TE-2A cases by having individually subnormal neuropsychological test results that substantiated organic brain involvement. The TE-2A and TE-2B subjects had been solvent-exposed between 7 and 35 years (mean 22) and 7 and 44 years (mean 23), respectively. The exposure magnitude, estimated as cumulative dose, was similar in the 2 groups (7). The TE groups were compared with previously unexposed age- and education-matched male referents. Each of the 3 groups comprised 12 subjects.

All the subjects had completed a comprehensive medical work-up to secure the absence of any other significant disease. A supplementary health check-up was also performed on each day of exposure challenge. Any kind of temporary illness, including the common cold, was not allowed for a period of 2 weeks preceding the chamber challenges. Olfactory function was checked qualitatively 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 threshold was also assessed quantitatively with n-butanol as the test odorant, with a procedure slightly modified from that described by the Connecticut Chemosensory Clinical Research Center (8). Of the 36 subjects, 32 were norosmic. One subject in each TE group and 2 referents showed hyposmia.

The subjects were informed that all the exposures were below current Swedish occupational exposure limits, and they were told about the duration of a session. Other details of the exposure design, such as the number or names of substances, were not disclosed until all the subjects had completed both sessions. The Ethics Committee of the Lund University (LU 94-236) approved the study, and all the participants gave their written consent to participate.

**Experimental design**

After careful consideration, a sequence of increasing exposure levels was chosen instead of a randomized exposure sequence, to avoid the possibility that the responses in phases with no or low exposure following phases with higher exposure would reflect remaining or delayed effects of the preceding high exposure. First, an initial chamber period without any chemical exposure was used to check for possible anxiety or suggestion effects introduced by simply entering an enclosed chamber environment where subjects might expect exposure to occur. The performance in this “zero phase” was compared with the performance outside the chamber (ie, in an ordinary office environment) during a preceding prechamber training session. Second, so that conditions would resemble an exposure situation commonly described by hyper sensititvity subjects as eliciting symptoms, it was considered important that the exposure should start at a very low exposure level, unlikely to provoke annoyance or reduce the performance of healthy subjects. Third, to counteract sensory adaptation effects, a sequence of consecutively increasing exposure levels was considered suitable. Thus solvent exposure started at 3 ppm (11 mg/m³ toluene or 14 mg/m³ BuAc) and followed a geometric progression scale with a ratio of 2 until reaching 48 ppm (180 mg/m³ toluene or 228 mg/m³ BuAc). The duration of the chamber phases was 20 minutes at 0 (zero) 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 minutes at 0 ppm (figure 1). The exposure was continuously monitored with an infrared spectrophotometer (Miran 1-A). Typically, the air concentration stabilized within 4 minutes after each increase and varied less than 10% at each exposure level. The exposure chamber had a volume of 2.15 m$^3$ (1.03 x 1.03 x 2.03 m). It had solid walls except for a glass front door. The chamber inlet was at floor level, and the outlet was in the ceiling. The turnover rate was 96 times/hour, and the chamber temperature varied between 20.4 and 23.5°C. The total time in the chamber was approximately 2 hours. Challenge responses (neurobehavioral tests) were collected during the zero phase, the 12 ppm phase, and the 48 ppm phase. In the middle of the latter 2 phases, the time-weighted average was typically 45 minutes at 7 ppm (26 mg/m$^3$ toluene or 33 mg/m$^3$ BuAc) and 75 minutes at 19 ppm (71 mg/m$^3$ toluene or 90 mg/m$^3$ BuAc).

**Challenge response**

Before entering the chamber, the subject was familiarized with the response procedures. This prechamber training session was carried out in a normal office environment where it was made sure that the instructions were understood and memorized. In the chamber the subject was seated comfortably, facing the glass door, with a small tabletop in front of him. During each of the 7 periods, a set of questions concerning smell intensity and annoyance-irritation was rated, as described elsewhere (5). The following tests of concentration and sustained attention were administered:

1. WAIS-R digit symbol (9). For the present study, 4 parallel versions with different digit-symbol key combinations were used.

2. The automated psychological test (APT) system (10), 2-way reaction time (RT2). The stimulus was a white square shown to the left or right side of a computer screen, using corresponding dual response keys. The individual results were expressed in terms of level (the mean of the 50 RT responses) and variation (the standard deviation of the 50 RT responses).

3. APT inhibition (RT-inhib). The test is similar to RT2 with the addition that the visual signal is accompanied by a randomly appearing auditory alarm (ratio 0.50), whereupon the subject was required to inhibit the response. Individual results were expressed as for RT2, with the addition of an error ratio (false hits).

The tests were given in the preceding order in the prechamber training phase and the zero phase, but during the 12-ppm phase and the 48-ppm phase the digit symbol test was completed last.

**Data analysis**

Data were analyzed in SPSS 8.0 for Windows. The 4 reaction-time variables were subjected to logarithmic transformation to improve the distributions satisfactorily to fit normality. The following 2 separate analyses were done on each of the 6 test variables: (i) performance was compared across the 3 chamber phases to assess the impact of increasing chemical challenge and (ii) performance in phases without chemical exposure was compared, that is, the prechamber training phases and the chamber zero phases. The latter analyses were focused on sessions (first versus second) and not on substances, since chemical exposure did not occur in the initial phases. The exposure sessions formed a repeated-measures design, counterbalanced within groups with respect to time of day (morning-afternoon), substance sequence, and test leader (5). The repeated-measures analysis of variance (ANOVA) of the SPSS general linear modules was applied. A full factorial balanced model was used (ie, including all higher-order interactions, with a cell size of 12 for each tested variable and type III sums of squares, using subject group (TE-2A, TE-2B, referents) and exposure sequence (toluene-BuAc versus BuAc-toluene) as between-group factors and phases (prechamber phase, zero phase, 12-ppm phase, 48-ppm phase) and substances (BuAc, toluene) as within-group factors. Since the interaction phase by subject group was of particular interest, a smaller model was also tested, excluding the factor exposure sequence, which, however, did not alter the main results and only strengthened the statistical power marginally and therefore is not presented here. Where appropriate, the Greenhouse-Geisser corrected results are reported. Only when statistically significant interactions appeared between any combination of factors in the ANOVA analysis were t-tests (paired or independent due to the nature of the data) used for further investigations. Statistical significance was assumed at an alpha level of $P=0.05$. 

![Figure 1. Phase duration and exposure levels during an exposure session (exposure schedule excluding the delay during exposure increase/decrease).](image-url)
Psychological test performance during experimental challenge

Results

Comparisons of responses across the chamber phases

The RT2 level and variation increased (deteriorated) during the chamber phases (Table 1). The digit symbol scores increased (improved) during the phases (Table 2). The RT-inhib variables were not clearly affected by the phase (Table 3). Neither substance nor exposure sequence showed an effect on any of the test variables. The increase (deterioration) in the RT2 level was more pronounced during the challenge to BuAc than during the challenge to toluene (ANOVA interaction phase by substance, P=0.046). The RT2 level increased the most clearly in the TE groups (ANOVA interaction phase by subject group, P=0.040). Posthoc analyses showed these

Table 1. Two-way reaction time scores on the automated psychological test during the prechamber and challenge phases (TE-2A and TE-28 = toxic encephalopathy, type 2A and 2B, respectively).

| Referents (N=12) | TE-2A (N=12) | TE-2B (N=12) | ANOVA P-values |
|-----------------|--------------|--------------|----------------|
|                 | Mean         | SD           | Mean           | SD             | Comparisons within groups | Comparisons between groups |
| Phase           | Substance    | Subject      | Sequence       |                | Prechamber phase versus zero phase | Chamber phases |
| Reaction time 2, level (ms) |              |              |                |                  | Prechamber phase versus zero phase | Chamber phases |
| n-Butyl acetate |              |              |                |                  | Prechamber phase versus zero phase | Chamber phases |
| Prechamber      | 312          | 24           | 350            | 45              | 347                      | 47                  |
| Zero phase      | 336          | 24           | 377            | 55              | 365                      | 57                  |
| 12 ppm          | 347a         | 27           | 411a           | 63              | 429a                     | 108                 |
| 48 ppm          | 348          | 26           | 424a           | 75              | 452a                     | 135                 |
| Toluene         |              |              |                |                  | Prechamber phase versus zero phase | Chamber phases |
| Prechamber      | 313          | 31           | 348            | 48              | 358                      | 53                  |
| Zero phase      | 340          | 32           | 389            | 73              | 375                      | 76                  |
| 12 ppm          | 339          | 31           | 421a           | 99              | 415a                     | 91                  |
| 48 ppm          | 339          | 26           | 411            | 98              | 415                      | 55                  |
| Reaction time 2, variation (ms) |              |              |                |                  | Prechamber phase versus zero phase | Chamber phases |
| n-Butyl acetate |              |              |                |                  | Prechamber phase versus zero phase | Chamber phases |
| Prechamber      | 50           | 8            | 62             | 18              | 63                       | 11                  |
| Zero phase      | 48           | 6            | 70             | 22              | 57                       | 12                  |
| 12 ppm          | 51           | 9            | 73             | 18              | 81a                      | 31                  |
| 48 ppm          | 48           | 8            | 89b           | 27              | 98c                      | 42                  |
| Toluene         |              |              |                |                  | Prechamber phase versus zero phase | Chamber phases |
| Prechamber      | 48           | 12           | 66             | 18              | 65                       | 12                  |
| Zero phase      | 48           | 10           | 69             | 20              | 63                       | 11                  |
| 12 ppm          | 51           | 11           | 88             | 59              | 131                      | 87                  |
| 48 ppm          | 53           | 13           | 77             | 40              | 90                       | 57                  |

a P<0.05, posthoc t-test, exposure phase compared with the zero phase.
b P<0.005, posthoc t-test, exposure phase compared with the zero phase.
c P<0.05, posthoc t-test, 48 ppm compared with 12 ppm.

Table 2. Raw scores of the digit symbol test during the prechamber and challenge phases (TE-2A and TE-2B = toxic encephalopathy, type 2A and 2B, respectively).

| Referents (N=12) | TE-2A (N=12) | TE-2B (N=12) | ANOVA P-values |
|-----------------|--------------|--------------|----------------|
|                 | Mean         | SD           | Mean           | SD             | Comparisons within groups | Comparisons between groups |
| Phase           | Substance    | Subject      | Sequence       |                | Prechamber phase versus zero phase | Chamber phases |
| n-Butyl acetate |              |              |                |                  | Prechamber phase versus zero phase | Chamber phases |
| Prechamber      | 62.1         | 12.6         | 48.6           | 13.3           | 47.0                      | 11.3                 |
| Zero phase      | 63.1         | 12.2         | 47.9           | 12.7           | 45.4                      | 11.6                 |
| 12 ppm          | 67.5a        | 13.3         | 47.8           | 11.5           | 46.7                      | 11.1                 |
| 48 ppm          | 68.3a        | 12.7         | 49.0           | 12.1           | 46.9                      | 12.3                 |
| Toluene         |              |              |                |                  | Prechamber phase versus zero phase | Chamber phases |
| Prechamber      | 63.5         | 13.1         | 46.7           | 15.5           | 46.7                      | 12.8                 |
| Zero phase      | 65.6         | 12.5         | 47.7           | 16.5           | 47.2                      | 13.4                 |
| 12 ppm          | 65.6         | 11.2         | 49.5           | 16.2           | 46.2                      | 11.5                 |
| 48 ppm          | 66.9a        | 13.4         | 50.2           | 16.3           | 45.1                      | 10.5                 |

a P<0.05, posthoc t-test, exposure phase compared with the zero phase.
b P<0.005, posthoc t-test, exposure phase compared with the zero phase.
Table 3. Inhibition reaction time scores on the Automated Psychological Test during the prechamber and challenge phases (TE-2A and TE-2B = toxic encephalopathy, type 2A and 2B, respectively).

|                      | Referents (N=12) | TE-2A (N=12) | TE-2B (N=12) | ANOVA P-values |
|----------------------|------------------|--------------|--------------|----------------|
|                      | Mean  | SD  | Mean  | SD  | Mean  | SD  |                          | 
|                      |       |     |       |     |       |     | Phase | Sub- | Subject | Se-     |
|                      |       |     |       |     |       |     |        | stance | group | quence |
| Reaction time inhibition level (ms) |        |     |       |     |       |     | Comparisons within groups |   | Comparisons between groups |     |
| n-Butyl acetate      |        |     |       |     |       |     |        |       |        |        |
| Prechamber           | 356   | 45  | 439   | 90  | 450   | 9   | 0.007  | 0.77  | 0.005  | 0.91   |
| Zero phase           | 348   | 38  | 423   | 63  | 427   | 104 |        |       |        |        |
| 12 ppm               | 358   | 37  | 451   | 86  | 452   | 110 |        |       |        |        |
| 48 ppm               | 361b  | 41  | 446   | 90  | 470   | 132 |        |       |        |        |
| Toluene              |        |     |       |     |       |     |        |       |        |        |
| Prechamber           | 358   | 35  | 438   | 111 | 463   | 100 |        |       |        |        |
| Zero phase           | 348   | 43  | 432   | 94  | 427   | 93  |        |       |        |        |
| 12 ppm               | 351   | 53  | 454   | 116 | 423   | 82  |        |       |        |        |
| 48 ppm               | 345   | 50  | 437   | 125 | 425   | 74  |        |       |        |        |
| Reaction time inhibition variation (ms) |        |     |       |     |       |     |        |       |        |        |
| n-Butyl acetate      |        |     |       |     |       |     |        |       |        |        |
| Prechamber           | 47    | 20  | 73    | 22  | 77    | 24  | 0.37   | 0.90  | <0.001 | 0.60   |
| Zero phase           | 40    | 12  | 83    | 21  | 80    | 32  |        |       |        |        |
| 12 ppm               | 44    | 21  | 85    | 62  | 81    | 23  |        |       |        |        |
| 48 ppm               | 41    | 16  | 78    | 35  | 98    | 54  |        |       |        |        |
| Toluene              |        |     |       |     |       |     |        |       |        |        |
| Prechamber           | 42    | 9   | 70    | 33  | 74    | 18  | 0.30   | 0.25  | <0.001 | 0.64   |
| Zero phase           | 39    | 9   | 73    | 27  | 76    | 25  |        |       |        |        |
| 12 ppm               | 41    | 16  | 81    | 37  | 75    | 19  |        |       |        |        |
| 48 ppm               | 36    | 9   | 71b   | 41  | 81    | 34  |        |       |        |        |
| Reaction time inhibition error ratio (%) |        |     |       |     |       |     |        |       |        |        |
| n-Butyl acetate      |        |     |       |     |       |     |        |       |        |        |
| Prechamber           | 2.7   | 3.1 | 4.3   | 4.3 | 10.3  | 7.9 | 0.006  | 1.0   | 0.003  | 0.59   |
| Zero phase           | 1.0   | 1.8 | 3.7   | 3.8 | 5.3   | 3.6 |        |       |        |        |
| 12 ppm               | 2.3   | 2.1 | 3.7   | 4.7 | 6.7   | 4.3 |        |       |        |        |
| 48 ppm               | 1.7   | 2.7 | 4.0   | 4.5 | 9.7   | 10.4|        |       |        |        |
| Toluene              |        |     |       |     |       |     |        |       |        |        |
| Prechamber           | 5.7   | 5.0 | 3.0   | 1.8 | 7.7   | 5.2 | 0.47   | 0.72  | 0.001  | 0.44   |
| Zero phase           | 1.7   | 2.7 | 3.7   | 3.6 | 5.7   | 5.8 |        |       |        |        |
| 12 ppm               | 1.7   | 3.6 | 2.7   | 3.1 | 9.7   | 10.6|        |       |        |        |
| 48 ppm               | 1.3   | 2.0 | 2.3   | 2.1 | 7.7   | 12.1|        |       |        |        |

* P<0.05, posthoc t-test, exposure phase compared with the zero phase.

increases to appear mainly from the zero phase to the first exposure phase, and among the referents an increase was observed only during the BuAc challenge (table 1). The RT2 variation showed an interaction phase by subject group (ANOVA interaction, P=0.037), and the posthoc analysis revealed an increasing variation for the TE groups only, most clearly during the BuAc exposure (table 1). The RT-inhib level showed an interaction phase by substance (ANOVA interaction, P=0.015), and the posthoc analysis revealed an increase only during the BuAc exposure, reaching statistical significance only in the reference group (table 3). Across the various test variables, scores improved generally from the first to the second session (ANOVA interaction substance by exposure sequence; P-values between <0.001 and 0.018, except for the RT-inhib error ratio with P=0.082). No other effects were observed, except that the TE groups had clearly poorer scores for all the test parameters (ANOVA factor subject group, P<0.001 to 0.035) (tables 1—3), as expected in light of the known base-line differences (7).

Comparisons of the prechamber and chamber zero phase responses

The RT2 level increased (deteriorated) slightly from the prechamber training phase to the chamber zero phase, and the RT-inhib level and error ratio decreased (improved) slightly. The other test variables did not change from the training to the zero phase (tables 1—3). The scores were similar before the exposure to either substance, and the exposure sequence did not matter. The RT parameters, discounting RT2 variation, decreased (improved) from the 1st to the 2nd session, and likewise the digit symbol scores increased (improved) (ANOVA interaction substance by exposure sequence, P-values <0.001 to 0.030). The level parameter of the RT2 and RT-inhib tests showed further interaction (ANOVA interaction phase by substance by exposure sequence, P-values 0.019 and
0.022, respectively), indicating more pronounced changes in scores from the prechamber phases to the zero phases during the 1st session than during the 2nd. However, these changes were in different directions [RT2 level increased (deteriorated) and RT-inhib level decreased (improved), paired t-test: the first session both substances P<0.001]. The digit symbol scores increased (improved) markedly from the prechamber phase to the zero phase in the reference group during the first session (ANOVA interaction phase by substance by subject group by exposure sequence, P=0.044), the only improvement within sessions and groups reaching statistical significance (referents, paired t-test: P=0.010). No other effects were observed, except for the expected lower scores for most of the test measures in the TE groups due to known base-line differences (ANOVA factor subject group, P<0.001 to 0.08) (tables 1—3).

Discussion

The present results suggest that TE subjects are not more affected in cognitive performance than healthy men are by ongoing low-level toxic exposure affecting the central nervous system, even when exposure is perceived as unpleasant and subjectively disturbing. As commonly reported in cases of toxic encephalopathy (1, 11), the TE subjects under study had long-standing complaints of generalized hypersensitivity to chemical smells, involving subjective worsening of fatigue or cognitive problems (5). Nevertheless, our study does not provide an objective correlation with the subjective vulnerability. Nor was performance compromised by merely entering the enclosed chamber environment, that is, not affected by suggestion or situational tension.

As one of the aims of our study was to contribute to the development of techniques for the assessment of various subjective hypersensitivity reactions, and for the differentiation of such reactions from responses characteristic for acute neurotoxic effects, the exposure was intentionally kept below known thresholds for acute neurotoxic effects. BuAc, although it has a strong smell already at the levels used in this study, is not regarded as irritating (peripherally in mucous membranes) below 100 ppm (475 mg/m³) (12), and it is only mildly irritating at 700 mg/m³ (13). Narcotic effects to the central nervous system from exposure to BuAc have, to our knowledge, not been reported for humans at levels that can be sustained voluntarily due to the highly irritating effects on the mucous membranes. Toluene, on the other hand, has been shown in a number of studies to produce disturbances in the central nervous system of healthy subjects beginning at 100 ppm (375 mg/m³) after a few hours (14). The few controlled studies performed on subjects with long-term occupational exposure have not shown convincing evidence of a higher vulnerability of cognitive functions in comparisons with unexposed referents at a toluene concentration of 63 ppm for 6 hours (15) or at 100 ppm for 4 hours (16). The air concentrations in our study were between 3 and 24 ppm during most of the session, and only reached 48 ppm during 20 minutes, corresponding to a total average level of 22 ppm (82 mg/m³ BuAc or 104 mg/m³ toluene) during the 85 minutes of chemical exposure. Thus we can confidently exclude the possibility that neurotoxic effects were induced by the BuAc exposure, and neurotoxic effects were also unlikely to occur during the toluene exposure. However, if suffering from a truly physiological hypersensitivity to solvents, TE subjects might possibly have shown some evidence of deterioration already at these low levels of toluene exposure. Since BuAc exposure tended to be more provocative than toluene, such a hypothesis was not supported.

It is not surprising that the TE subjects reported higher annoyance levels than the referents (5), since expectancy or cognitive bias has been shown to influence perceived irritation and annoyance (17), and even healthy subjects often erroneously believe that their cognitive performance is negatively affected by exposure to annoyingly strong odors (18). Among TE patients, the chemical smells are likely to bring to mind situations of occupational exposure in the past, being associated with symptoms of intoxication and threats to health. The discrepancies found in a few of the test variables might have been due to higher levels of stress and fatigue, or a drop in motivation, among the slightly brain-damaged TE subjects, for whom the exposure provocation was likely to be more emotionally demanding or even threatening. The chronic brain dysfunction of TE subjects, as shown in the generally inferior base-line test scores, might have been a further contributory factor, by making the TE subjects more susceptible to stress reactions and less able to cope with them in an adaptive manner during the 2-hour stay in the chamber (19). To facilitate coping, the chamber sessions included frequent short periods of inactivity, allowing subjects leisure reading or relaxation at their own discretion. However, the design did not allow an analysis of the relative impact of the various possible determinants of fatigue independently of chemical exposure, for example, due to tension or task demands. Such an analysis would have required additional exposure sessions without chemical exposure, and preferably also sessions with intermittent zero phases. A randomization of the exposure levels throughout the sessions was considered to be a less suitable method when chemically hypersensitive subjects are being studied, since these subjects commonly report that the reduction in well-being and performance associated with exposure to chemical
smells lingers for some time after the exposure has decreased or been terminated. Thus the impact of any specific exposure level cannot be reliably studied with hypersensitive subjects by applying a sequence of randomized exposure levels. In addition, the very rapid decrease and increase in the exposure levels required for obtaining intermittent zero phases was not possible satisfactorily with the present technical equipment when the relatively large volume of the chamber is considered. Our results suggest that a substantially shortened exposure session design that includes such improvements may be possible.

We have previously reported that the 1st of the 2 sessions evoked the strongest annoyance reactions, irrespective of the substance used (5). This finding may have possibly been due to the subjects' expectancy of chemically induced annoyance, or it may have been caused by tension due to the complete novelty of the situation. The observed smoother performance on several cognitive tests during the 2nd session may have been explained by this kind of decreased expectancy of discomfort and lower situational tension. A general test-retest learning effect is less likely to have caused the improvement in reaction time from the 1st to the 2nd session, since such effects should have been discernible already during the 1st session as continuously improving reaction times, which was not the case. Only the digit symbol scores showed this kind of more-or-less continuous improvement during the sessions, and only in the reference group, in addition to the improvement from the 1st to the 2nd session, apparently indicating a learning effect.

A slight deterioration in the RT2 scores did occur, however, that was not restricted to the TE groups. There seems be no simple explanation for this observation in light of the nondeteriorating results across the other test variables. A sustained deterioration, that is, deterioration not only in the 12-ppm phase but also in the 48-ppm phase, was restricted to the BuAc exposure, a finding suggesting a psychological mechanism due to the more unpleasant and strong smell of BuAc than the smell of toluene. The RT2 task is probably the simplest and one of the least demanding tasks, often performed by subjects as continuously improving reaction times, which was not the case. Only the digit symbol scores showed this kind of more-or-less continuous improvement during the sessions, and only in the reference group, in addition to the improvement from the 1st to the 2nd session, apparently indicating a learning effect.

As expected on the basis of the previous individual neuropsychological examination results of each TE subject, the TE-2B subjects displayed less favorable scores for most of the test variables during the base-line conditions, that is, during the initial training outside the chamber and in the 1st chamber phase with zero exposure. However, also the 2A subjects showed deviations in 3 of the 6 test variables (RT-inhib level and variation, digit symbol), which might signify a slight organic dysfunction undetected in the initial clinical examination (7).

In the chamber challenge the air concentrations of the chemical substances were low and the exposure duration was short, but for a TE patient with reduced cognitive functioning, due to chronic brain impairment, any further reduction during the exposure may be very disturbing. Our study was performed under laboratory conditions considered to be fairly reassuring for the subject. However, in the everyday workplace environment the true risk implications of a perceived chemical exposure are often unknown to the individual and might easily be overestimated if the evolving symptoms are interpreted as being of toxic origin. This possibility underlines the caution necessary when one tries to extrapolate our results to actual worksite conditions. The concern for developing a chronic disease due to workplace conditions may act as a long-term stress factor that adds to and amplifies the burden of primary symptoms (20, 21). Worry about chemical exposure, together with increased annoyance reactions, may make work conditions mentally unacceptable in the long run, and this possibility should be taken into account when both the prospects of TE patients in maintaining gainful work and the situation for persons with subjective environmental hypersensitivity to chemicals are under consideration.

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