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Human response to controlled levels of toluene in six-hour exposures

by Ib Andersen, MD,¹ Gunnar R Lundqvist, MSc,² Lars Mølhave, MSc, PhD,² Ole Find Pedersen, MD,² Donald F Proctor, MD,³ Michael Væth, MSc, PhD,⁴ David P Wyon, PhD⁵

ANDERSEN I, LUNDQVIST GR, MØLHAVE L, FIND PEDERSEN O, PROCTOR DF, VÆTH M, WYON DP. Human response to controlled levels of toluene in six-hour exposures. *Scand j work environ health* 9 (1983) 405-418. The nasal mucus flow, lung function, subjective response, and psychometric performance of 16 young healthy subjects was studied during 6-h exposures to clean air and to 10, 40 or 100 ppm of toluene under controlled conditions. The toluene exposures did not affect nasal mucus flow or lung function. At 100 ppm irritation was experienced in the eyes and in the nose. There was a significant deterioration in the perceived air quality and a significant increased odor level during all exposures to toluene. The test battery investigated visual perception, vigilance, psychomotor functions, and higher cortical functions and comprised five-choice, rotary pursuit, screw-plate, Landolt's rings, Bourdon Wiersma, multiplication, sentence comprehension, and word memory tests. In these eight tests measuring 20 parameters, no statistically significant effects of the toluene exposure occurred. For three tests (multiplication errors, Landolt's rings, and the screw plate test) there was a borderline significance ($0.05\% < p < 0.10\%$). The subjects felt that the tests were more difficult and strenuous during the 100-ppm exposure, for which headache, dizziness, and feeling of intoxication were significantly more often reported. The exposures to 10 and 40 ppm did not result in any adverse effects.

Key terms: air quality, airway resistance, discomfort, environmental chamber, mucociliary clearance, odor, psychometric performance, rhinomanometry, subjective response.

Toluene is a chemical substance widely used in industry for the production of other chemicals and as a solvent for paints, inks, coatings, glues, etc. Painters and workers in the printing, rubber, and leather industries, as well as workers in many other industries, are exposed to this substance.

The biological effects of toluene are well documented (12, 20, 27). The narcotic and neurotoxic properties of this substance represent the main health hazards, but in very few studies have human subjects been exposed to toluene under controlled conditions and during periods comparable to a workday. Changes in behavior are normally considered the earliest manifestations of neurotoxicity. Only two studies, one Swedish and one Japanese, of toluene's behavioral effects have been performed under controlled exposure conditions. Gamberale & Hultengren (15) investigated reaction time and two tests of perceptual speed with 12 male students. They found no effects from 20-min exposure to 100 ppm, but performance was impaired at higher concentrations. Ogata et al (23), in a 7-h exposure of 23 male students to 100 ppm, found no effect on reaction time.

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The purpose of the present investigation was to study, during 6-h exposures, the effects of different concentrations of toluene on airway function in young healthy subjects with no former regular exposure to solvents, the discomfort created, and the ability to perform a range of manual and mental tasks simulating various aspects of industrial work. This project was carried out in order to establish dose-effect curves for these functions at the level of the hygienic standard and lower. The present hygienic standard for toluene is 100 ppm ($375 \text{ mg} \cdot \text{m}^{-3}$) both in the United States (3) and in Denmark (8).

Material and methods

Exposure facility

The study took place in an environmental chamber with walls of stainless steel at the Institute of Hygiene, Aarhus, Denmark.

Fig 1. Diagram of exposure chamber. (1 = intake of outdoor air, 2 = dust filters, 3 = charcoal filter, 4 = dehumidification unit, 5 = heating and cooling coils, 6 = air flow meter, 7 = fans, 8 = steam injection for humidification, 9 = heating coil, 10 = humidity controls, 11 = temperature control for room air, 12 = pressure control for room air, 13 = toluene detector, 14 = toluene vapor generator, 15 = toluene vapor injection system, 16 = temperature control for walls, 17 = chamber wall with thermal control system, 18 = inspection window, 19 = perforated floor, 20 = exposure chamber interior).

The chamber had a floor area of 29 m^2 and a volume of 83 m^3 . The design of the chamber is shown in fig 1. During the experiment the average air and globe temperature $\pm$ one standard deviation (SD) were 22.0 (SD 0.3) $^{\circ}\text{C}$ and 22.6 (SD 0.1) $^{\circ}\text{C}$, respectively; the relative humidity was 46 (SD 6) %, the air velocity was $10\text{--}20 \text{ cm} \cdot \text{s}^{-1}$; and fresh air was supplied at a rate of $420 \text{ m}^3 \cdot \text{h}^{-1}$. This level gave an air change rate of five per hour. The air change rate was measured by the dilution of a tracer gas – Krypton (Kr-78) – and checked continuously by measurement of the volume of intake air (fig 1, number 6). The fresh air supplied to the chamber was filtered through absolute dust filters removing 99.99 % of the particles and through charcoal filters removing organic gases and vapors. By means of a pressure pump (Milton Roy, Riviera Beach, FL, United States) toluene was injected through a heated nozzle in the air supply system (fig 1, number 15) to obtain concentrations of either 10, 40, or 100 ppm during one exposure day. The toluene used was spectroscopy grade and from the same production batch (Toluol, Merck, number 8331, 99.7 % pure).

The toluene concentration was monitored continuously by a photoionization detector (HNU 201, HNU System Inc, Newton, MA, United States). The detector was calibrated every second hour against a pressurized standard mixture of 106 ppm of toluene in dry air (150 bars or $15 \cdot 10^5 \text{ Pa}$) (Linde, Höllriegelskreuth, Federal Republic of Germany), and by 6-h sampling on charcoal tubes subsequently analyzed by gas chromatography (HP 5700, Hewlett-Packard, Avondale, PA, United States). Mixing of the air in the chamber was achieved by a recirculation loop with a flow rate of $1,400 \text{ m}^3 \cdot \text{h}^{-1}$. No vertical or horizontal concentration gradients were found in the chamber. The variations in toluene concentrations with time were always within 8 % of the planned value. No other components than toluene were found in the air by the gas chromatographic-mass spectrometry method, which has a detection limit of $0.1 \text{ mg} \cdot \text{m}^{-3}$. The dust concentration was measured during the exposure period by gravimetric methods. The filters were Sartorius $11107 \times 0.2 \mu\text{m}$ weighed on a microbalance Mettler ME22. The average dry dust concentration was 9.5 (SD 4.6) $\mu\text{g} \cdot \text{m}^{-3}$.

Subjects

The subjects exposed were 16 healthy Danish students. Their average age was 24 years, and the range from 21 to 32 years of age. All were males without any symptoms or signs of diseases. Three were smokers with a consumption of one to nine cigarettes per day. All were "nose breathers" and without any previous regular exposure to organic solvents.

Procedure

The subjects were in the chamber in groups of four for 8 h a day on four consecutive days. They were dressed in all-cotton work suits with an insulation value of 0.7 clo. Before the study each subject was trained in all procedures at a 2-h session. During the study the procedures were identical each day, the only variable being the concentration of toluene, which was either 0, 10, 40, or 100 ppm on the 4 d. No agents were used to mask the different odor levels each day. For the exposure of the four groups a balanced Latin-square design was used (see table 1). The subjects knew that they would be exposed to different concentrations of toluene at or below the level of the hygienic standard, but they were not told when, for how long, or how much.

The daily procedures are shown in fig 2. After acclimatization for 30 min in clean air in the chamber the subjects went through rhinomanometric measurements, forced

vital capacity measurements, and body plethysmography. These measurements served as controls each day (run 0). The 25 target words of a word memory test and a first questionnaire on discomfort were also presented then. After 1 h of clean air exposure in the chamber the concentration of toluene was steadily increased during 30 min to the concentration intended for the day. When the equilibrium concentration was reached, a second questionnaire on discomfort was presented. After 1 h of exposure all subjects went through all physiological, discomfort, and performance measurements for the next 1.5 h (run 1). After a 1-h lunch period in the chamber a similar second series of measurements was made during the fifth and sixth hours of exposure (run 2). Then the subjects left the chamber.

Physiological measurements

We measured the nasal removal of toluene from the inhaled air during 100-ppm exposure periods by drawing air through the

Table 1. Order of toluene concentrations (ppm) used for each group of four subjects.

Group	Day			
	1	2	3	4
1	0	10	40	100
2	10	0	100	40
3	40	100	0	10
4	100	40	10	0

Fig 2. Variation of the concentration of toluene with time during the four different exposures. Identical measurements were performed as indicated in the six rows below the time. In the word memory test words were presented in the morning, and word identification took place at the end of the exposure day.

nose by means of a pharyngeal sampling tube placed in the oropharynx and connected to the photoionization detector. The subject performed a Valsalva maneuver while a vacuum pump drew air through the subject's nose at a rate of $20 \text{ l} \cdot \text{min}^{-1}$. The toluene concentration in the end expiration air was measured by the collection of the air in a 50-ml gas-pipette and subsequent analyses by gas chromatography.

Nasal mucociliary flow was measured by external detection of a technetium $^{99\text{m}}$ -labeled resin particle (diameter 0.6 mm) placed on the superior surface of the inferior turbinate and by the passage time of a saccharin-dye particle from this position to the oropharynx. Nasal flow resistance was measured through an oronasal mask with a pneumotachometer (Mercury, Glasgow, United Kingdom) attached. Forced expiratory vital capacity (FVC), forced expiratory volume in the first second after maximal inspiration ($\text{FEV}_{1.0}$), and forced expiratory flow during exhalation of the middle part of FVC (FEF_{25-75}) were measured with a single breath instrument (Vitalograph®, Buckingham, United Kingdom). These techniques have been described in detail earlier (5, 6, 7). Functional residual capacity and airway resistance were measured in a whole-body plethysmograph (Mercury) (13, 14).

Subjective discomfort

Subjective estimates of discomfort were obtained with the following procedure: The subjects were asked to place a mark on a continuous scale with end points defined by a verbal description. The votes were read by us as the percentage of the full scale. The subjects were asked to estimate air temperature, humidity, air movements, light intensity, noise level, air quality, odor level, fatigue, sleepiness, work strain, difficulty of work, effort, and speed of reaction. In the same way they were asked about irritation of the eyes, nose, throat, and lower airways and about coughs, headache, feeling of intoxication, dizziness, and nausea.

Performance tests

Eight different performance assessment tests were used to cover different skills.

All tests were performed twice each day, once in each of the two runs (runs 1 & 2) during the exposure period. For the "pencil and paper tests" eight different parallel versions of each test were available.

The five-choice serial reaction test has been described by Poulton (24) and has been used extensively to measure the effects of heat, noise, alcohol, etc, upon perseverance and concentration. The subject uses a metal probe to touch five small targets in a continuous random sequence given by a five-lamp display. Two further aspects were added in our test to measure aiming and vigilance – responses initially missing the targets were recorded (aiming) and the subject had to press a hand-held button to report brief, barely visible delays automatically introduced at random in 5 % of the events (vigilance). Data for each response were recorded on a paper-tape punch during the 35-min test period. The test was self-paced. In the analysis we looked at eight different measures (as listed in table 4 of the Results section).

In the rotary pursuit test the subject tries to maintain a hand-held probe on a small target near the periphery of a rapidly rotating Gramophone type of turntable. Time on target was recorded on a counter during five 20-s periods with 10-s rest periods in between. The task demands coordination between vision and arm movements; it is sensitive to heat and cold (26).

In the screw-plate test the subject transfers small nuts and bolts between holes in an aluminum plate. Thirty-two nuts and bolts were transferred during each test, and the time was measured. Half of the nuts were on one side and half on the other to equalize the advantage for left- and right-handed subjects. Coordination between vision and finger movements is important in this test. A test along similar lines has been used to test the manual dexterity of divers under water (10) and in the cold (18). The present version, in which the screw-plate stands on a transverse flange, leaving both hands free, was developed by Wyon et al (29).

In Landolt's ring test a card is presented with 100 small circles, of which 50 % have a gap oriented in random directions. The subjects should mark the broken rings with a pencil. The time used and the number of errors were recorded. The present test, using the classic Landolt rings not to

determine threshold acuity but to construct a visually demanding repetitive performance task, was first used by Löfberg et al (19). All our subjects performed a vision test before the study, and some had to use glasses to obtain normal vision. The light intensity at table level was 300 lx, and the subject's head was fixed at reading distance during this and the following test, which too simulates the performance of a repetitive task placing some demands on visual acuity and perception.

The Bourdon Wiersma test is of a similar design. In it a paper with 175 three-, four-, and five-dot figures at random is presented. The subjects mark the four-dot figures with a pencil. The time used and the number of errors were recorded (17).

Finally the higher cortical functions were examined with three tests. In the multiplication test two three-digit random numbers were to be multiplied. All six digits were different, and no zeros occurred. There were 25 of these units in each test. The time used to complete one sheet and the number of errors were recorded.

In the sentence comprehension test the subjects worked through a typed list of 75 statements, marking them as true or false. The statements were a Danish translation of the reasoning test first used by Baddeley (9), and were of the following kind:

Statement	Problem	Answer
A follows B	BA	true/false
B is not preceded by A	AB	true/false

The answers to these two statements are true and false, respectively. The statements were selected in a random sequence from 96 possible choices using four sentence constructions that could also be negated, the two letters used being a combination of two of the following three: A, B, C. The passive voice, being uncommon in Danish, was not used. The time taken to complete the test and the errors were recorded.

In the word memory test a list of 25 common words was presented visually and simultaneously to all the subjects, who read each word aloud in unison with the experimenter. The list was removed, and 6 h later the subjects were presented with a list containing 50 common words, including the 25 "target words." The number of target words correctly identified was re-

corded together with omissions and incorrect identifications, allowing a signal detection analysis as described earlier (28). The results are expressed as word memory area and word memory beta.

Statistical methods

The data from each test were examined by analysis of variance techniques (11), using the GENSTAT system (2). To ensure that the assumptions of the statistical method (normal error distribution, homogeneity of variances) were correct, untransformed measurements and two transformations of the data (log and square root) were considered in an initial analysis of each set of test results. The appropriate transformed measurements were used in the subsequent statistical analysis.

In the statistical model a measurement was described as a sum of a systematic component and a random component. The systematic component represented the part of the measurement which could be explained by the design; it contained the following factors: exposure, day (representing a possible effect of learning), group (see table 1) and run, the last factor referring to the measurement period within a day (fig 2). The random component consisted of three terms representing, respectively, the intersubject random variation (U), the intrasubject random variation between days (V), and the intrasubject and intraday random variation between runs (X). A few of the analyses required an additional random term describing the intrasubject random variation between runs (W). The random terms were assumed to be statistically independent with means of zero and variances of σ_U^2 , σ_V^2 , σ_W^2 and σ_X^2 .

In the statistical analysis the influence of each of the factors in the design was tested against an appropriate error term by a standard F-test. For each test the results of the analysis of variance were summarized in an analysis-of-variance table of the form shown in tables 2 and 3. Table 2 was used for the measurements obtained twice a day during the period of exposure (the performance tests, the word memory test, and the subjective evaluation of work conditions). For the mean squares the sum of and the difference between the two daily measurements from each subject were computed, and analyses of variance were

Table 2. Results of the analysis of variance used to summarize the statistical analysis of the performance tests, the word memory tests, and the subjective evaluation of the work conditions. (For description, see text).

Source of variation	Degrees of freedom	Mean square	Variance ratio
<i>Stratum 1: subjects</i>			
Group	3	S_1^2	S_1^2/S_2^2
Residual (error 1)	12	S_2^2	
[Expected value: $8\sigma_U^2 + 2\sigma_V^2 + \sigma_X^2 (8\sigma_U^2 + 2\sigma_V^2 + 4\sigma_W^2 + \sigma_X^2)$]			
<i>Stratum 2: subjects · days</i>			
Day	3	S_3^2	S_3^2/S_9^2
Exposure			
Total	3	S_4^2	S_4^2/S_9^2
Linear	1	S_5^2	S_5^2/S_9^2
Deviation from linearity	2	S_6^2	S_6^2/S_9^2
Group · day	6	S_7^2	S_7^2/S_9^2
Residual (error 2)	36	S_8^2	
(Expected value: $2\sigma_V^2 + \sigma_X^2$)			
<i>Stratum 3: subjects · days · runs</i>			
Run	1	S_9^2	S_9^2/S_{16}^2 (S_9^2/S_{17}^2)
Run · group	3	S_{10}^2	S_{10}^2/S_{16}^2 (S_{10}^2/S_{17}^2)
Run · day	3	S_{11}^2	S_{11}^2/S_{16}^2 (S_{11}^2/S_{18}^2)
Run · exposure			
Total	3	S_{12}^2	S_{12}^2/S_{16}^2 (S_{12}^2/S_{18}^2)
Linear	1	S_{13}^2	S_{13}^2/S_{16}^2 (S_{13}^2/S_{18}^2)
Deviation from linearity	2	S_{14}^2	S_{14}^2/S_{16}^2 (S_{14}^2/S_{18}^2)
Run · day · group	6	S_{15}^2	S_{15}^2/S_{16}^2 (S_{15}^2/S_{18}^2)
Residual (error 3)	48	S_{16}^2	
(Expected value: σ_X^2)			
Residual subject · run	(3a) 12	S_{17}^2	S_{17}^2/S_{18}^2
(Expected value: $4\sigma_W^2 + \sigma_X^2$)			
Residual subject · day · run	(3b) 36	S_{18}^2	
(Expected value: σ_X^2)			

Table 3. Results of the analysis of variance used to summarize the statistical analysis of the simple exposure contrast in the airway resistance measurements and the subjective discomfort evaluations. (For description, see text).

Source of variation	Degrees of freedom	Mean square	Variance ratio
Run	1	S_1^2	S_1^2/S_8^2 (S_1^2/S_9^2)
Run · group	3	S_2^2	S_2^2/S_8^2 (S_2^2/S_9^2)
Run · day	3	S_3^2	S_3^2/S_8^2 (S_3^2/S_{10}^2)
Exposure			
Total	3	S_4^2	S_4^2/S_8^2 (S_4^2/S_{10}^2)
Linear	1	S_5^2	S_5^2/S_8^2 (S_5^2/S_{10}^2)
Deviation from linearity	2	S_6^2	S_6^2/S_8^2 (S_6^2/S_{10}^2)
Run · day · group	6	S_7^2	S_7^2/S_8^2 (S_7^2/S_{10}^2)
Residual	48	S_8^2	
Residual subject · run	12	S_9^2	S_9^2/S_{10}^2
Residual subject · day · run	36	S_{10}^2	

applied to these sums and differences. The mean squares thus obtained were exactly twice the corresponding mean-square values given in table 2. The analysis of the sums gave the mean-square values in strata 1 and 2, while the corresponding values in stratum 3 were obtained from the analysis of the differences.

The analysis-of-variance table contains the main effects and interactions considered in the statistical analysis. The inter-

actions are indicated by a dot between the factors involved. The sum of squares ascribed to the exposure factor was further subdivided into a sum of squares for linear trend in dosage and a sum of squares for deviation from linearity. The interaction between run and exposure was treated in a similar manner. The additional random term W was introduced in the statistical model if the variance ratio S_{17}^2/S_{18}^2 differed significantly from 1. In this case the third

stratum split up into two strata, and the appropriate variance ratio tests were those given in parentheses.

The experimental design did not allow an estimation of all potentially interesting interaction terms; especially the exposure-day interaction and the exposure-group interaction were confounded with the group-day interaction and hence could not be estimated with the present design.

The statistical analysis of the lung function measurements, for which daily control measurements (run 0) were available, were summarized in an analysis of variance table almost identical to table 2. In this case the degrees of freedom in stratum 3 were doubled and $2\sigma_v^2$ was replaced by $3\sigma_v^2$ in the expression for the expected values of the residual variation. In this case the mean-square values in strata 1 and 2 were obtained as three times the corresponding mean squares in an analysis of variance of the average daily measurement. To derive the remaining mean-square values, the differences run 1 - run 0, run 2 - run 0, and run 2 - run 1 between measurements from the same subject on the same day were calculated, and analyses of variance were applied to these differences. The mean-square values in stratum 3 were then obtained as the average of the corresponding mean squares in these three analyses. The presence of a daily control measurement implied that the effect of exposure could be tested against the intrasubject random variation on the same day (stratum 3). This aspect was further explored by an analysis of variance, shown in table 3, of the simple exposure contrast given as the difference between the average measurement during exposure and the control measurement.

The statistical analyses of the subjective discomfort evaluation obtained four times a day (see fig 2) were summarized with the analysis of variances in table 3. The analysis was based on the differences between the average score during exposure and the control score. However, the discomfort evaluations relating to irritation of the eyes, nose, throat, and lower airways, as well as cough, headache, feeling of intoxication, dizziness, and nausea, were not suitable for an analysis of variance. Instead the four differences between the average score during exposure and the control score were ranked

for each subject, and nonparametric statistical methods (Friedman's test and van Elteren's test) were applied to evaluate the effect of exposure.

The reliability of the tests used in this experiment was evaluated through correlation coefficients between measurements obtained in runs 1 and 2. Two correlations, reflecting different aspects of the correlation structure, were calculated, namely,

$$r_1 = (s_U^2 + s_V^2)/(s_U^2 + s_V^2 + s_X^2)$$

and

$$r_2 = (s_V^2)/(s_V^2 + s_X^2),$$

where the estimates s_U^2 , s_V^2 and s_X^2 were derived from the set of equations obtained from setting the expected values of the error terms equal to the corresponding mean squares. If the additional random term was needed in the model, the formulas above should be modified by the addition of s_W^2 in the denominators. The correlation coefficient r_1 gives the correlation between runs 1 and 2 (corrected for the influence of the systematic factors) from different subjects, while r_2 gives the correlation between run 1 and run 2 measurements (corrected as above) from the same subject on different days.

Our level of significance was 5 %.

Results

Test reliability

The reliability of the tests was evaluated through correlation coefficients between measurements obtained in run 1 and run 2. The two correlation coefficients r_1 and r_2 for each test reflect the group and individual reproducibility of the test, respectively. The group reproducibility was excellent for the vitalograph measurements ($r_1 = 0.98$), whereas less acceptable group reproducibilities ($r_1 < 0.78$) were found for the five-choice test (choice error rate and false button press rate), the number of errors in Bourdon-Wiersma, and word memory beta. An even less acceptable group reproducibility ($r_1 < 0.70$) was found for the body plethysmographic measurements and for subjective voting on work difficulty and impression of reaction time.

The individual reproducibility r_2 was in general small, indicating a pronounced

daily personal variability for most tests. The only tests with an r_2 bigger than 0.50 were the rhinomanometric measurements and memory area.

Physiological measurements

The concentration of toluene in the pharyngeal air during 100-ppm exposure was not different from the concentration in the room air. The detection limit of the method was 5 ppm, corresponding to 5 % of the values measured, and we conclude that only little, if any, absorption took place in the nose. The average concentration ($\pm$ one standard deviation) of toluene in the end expiratory air measured by a gas bag method after 6 h of exposure was 29 (SD 4.0) % of the room air concentration.

Nasal mucus flow was measured with the tagged particle technique and with the saccharin/dye transit time measurement. With the first technique we found the average flow in the anterior and posterior third of the nose to be $0.6 \text{ cm} \cdot \text{min}^{-1}$, whereas flow in the middle third was $0.9 \text{ cm} \cdot \text{min}^{-1}$. There was no significant change from control values during any of the three exposures to toluene. This result applies to all five measuring points in the nose. The transit times for the dyed saccharin particles were from 6 to 18 min for 15 of the subjects, the average being 10 min. One subject had a transit time of 25 min. The toluene exposure did not affect the transit time. There were no differences between smokers and non-smokers.

Fig 3. Variation of the subjects' average perception of the odor with time during the four different exposures to toluene. The voting scale is from "no odor" = 0 to "strong odor" = 100.

Fig 4. Variation of the subjects' average impression of the air quality with time during the four different exposures to toluene. The voting scale is from "fresh air" = 0 to "bad air quality" = 100.

The average pressure drop across the nasal cavity at 40 and 60 l·min⁻¹ was 26.2 (SD 3.8) mm of H₂O and 44.0 (SD 5.8) mm of H₂O, respectively. FVC, FEV_{1.0} and FEF₂₅₋₇₅ were 5.4 (SD 0.8), 4.7 (SD 0.8), and 5.0 (SD 1.1) l·s⁻¹, respectively. Functional residual capacity and airway resistance were 5.2 (SD 1.0) l and 0.9 (SD 0.3) cm of H₂O l⁻¹·s. None of these parameters changed significantly with the exposure time or concentration.

Subjective discomfort

All the subjects found the temperature, humidity, air velocity, light, and noise levels comfortable under all conditions. No statistically significant effects of toluene concentration on the subjective judgments of these factors could be shown.

Air quality and odor level were the only climate descriptors that significantly correlated with the air concentrations of toluene. When the toluene concentration increased, the subjects felt that the air quality deteriorated and the odor level increased.

The subjects' average impression of the odor level during the day is shown in fig 3. It appears that the air is almost odorless under control conditions (0 ppm) and on the first evaluation each day (0 ppm). After an initial high odor estimation an adaptation phenomenon is seen during all the exposures; it is more pronounced in the first part than during the second part of the exposure period. The odor adaptation is more pronounced than the air quality adaptation. At all toluene concentrations the odor impression was significantly different from that of the control condition. At the 100-ppm exposure level three subjects found the odor unacceptable, whereas all the subjects found the odor acceptable at the other exposure levels.

The voting of the subjects on irritation of the eyes, the nose, the throat, and the lower airways showed that during the 100-ppm exposure a statistically significant irritation was experienced in the eyes and in the nose, but not in the throat or in the lower airways. On the average, irritation never exceeded 13 on a scale with a maximum value called strong irritation (= 100); the highest individual estimation was 64. Six subjects did not report any

irritation during the 100-ppm exposure. In general the irritation therefore may be described as slight. The irritation was felt just after the exposure began and was constant throughout the exposure day.

The subjects did not experience nausea nor did they cough. There was a statistically significant increase in the occurrence of headache, dizziness, and feeling of intoxication during the 100-ppm exposure, but not during exposure to the other concentrations. This phenomenon was experienced by about half of the subjects, and the intensity was slight to moderate.

The subjects' impression of the quality of the air is given in fig 4. They felt that the air quality was significantly lower during all toluene exposures than in clean air. The air quality deterioration was more pronounced at the higher toluene concentrations. Some adaptation occurred, but it was less than the odor adaptation. During the 100-ppm exposure three subjects found the air quality unacceptable. At the lower exposures all subjects considered the air quality acceptable.

The subjects felt that the work was more strenuous during the 100-ppm exposure than during the other exposures. The subjects also had the impression that their reaction time was prolonged during the toluene exposures. These effects were statistically significant. There was no effect of toluene concentration on the subjects' expressed interest in the work or on their mood, fatigue, and sleepiness.

Symptoms or complaints other than those already mentioned were never reported even though space was available for such reports in the questionnaire.

Performance tests

In table 4 the arithmetic means and the standard errors of the means after 5 h of exposure to clean air are given for the different parameters measured in the five-choice test, and the results of an analysis of variance are given in table 5. From this table it can be seen that no effects of the toluene exposures were found for any of the five-choice test parameters. There was a significant interaction between exposure and time on day (run).

The average results of the other performance tests after 5 h of exposure to clean air are shown in table 6, and the results

of an analysis of variance are given in table 7. There was a borderline correlation ($0.05 < p < 0.10$) between toluene and the

results of the screw-plate test, Landolt's ring test, and the number of errors in multiplication.

No effects of toluene concentration on other tests could be shown. All tests were significantly affected by learning.

Table 4. The arithmetic means of the five-choice test parameters after 2- and 5-h exposure to clean air. For the latter exposure the standard error of the mean is also given.

Test parameters	Arithmetic mean	Standard error of the mean
Ordinary taps per 1,000 s	1,079	45
Wrong targets per 1,000 taps (CER)	3.24	0.42
Plate taps per 1,000 taps	50.4	10.7
False button presses per 1,000 taps	1.81	0.47
True button presses per 1,000 delays	693	62
Reaction gaps > 1.5 s per 1,000 taps	85.3	21.4
Reaction time (s) without button presses	0.955	0.046
Reaction time (s) with button presses	1.681	0.087

Discussion

Despite the wide use of toluene in industry only a few experimental exposures have been performed at or below the present hygienic standard of 100 ppm (1, 15, 21, 23, 25). Only very few subjects have participated in these studies, and the impurities in the toluene used have not been measured. In our study with 16 subjects we intended to imitate the conditions in the workplace with 6-h exposure periods and with subjects constantly participating in tests or physiological measurements. We exposed the subjects to toluene under

Table 5. Results of the analysis of variance on the five-choice test data. (OT = ordinary taps per 1,000 s, CER = wrong targets per 1,000 taps, PTR = plate taps per 1,000 taps, FBR = false button presses per 1,000 taps, TBR = true button presses per 1,000 delays, RG = reaction gaps > 1.5 s per 1,000 taps, RT - BP = reaction time (s) without button presses, RT + BP = reaction time (s) with button presses, r = correlation coefficient)

Source of variation	Degrees of freedom	OT (s ²)	CER (s ²)	PTR (s ²)	FBR (s ²)	TBR (s ²)	RG (s ²)	RT - BP (s ²)	RT + BP (s ²)
Group	3	291,500	3.507	10,196	1.419	349,700	4.998	0.3100	0.2007
Error 1	12	117,500	2.740	10,585	5.588	577,000	3.234	0.1338	0.1857
Day	3	124,650***	0.895	5,342***	0.519	130,000***	0.648**	0.1102***	0.3444***
Exposure									
Total	3	1,494	0.950	638	0.227	10,104	0.045	0.0010	0.0018
Linear	1	675	0.024	55.5	0.019	2,232	0.004	0.0012	0.0005
Deviation from linearity	2	1,904	0.131	929	0.340	14,040	0.065	0.0010	0.0024
Group · day	6	11,120*	0.260	1,101	0.650	33,325	0.173	0.0092*	0.0127
Error 2	36	3,757	0.464	614	0.467	17,830	0.115	0.0034	0.0102
Run	1	26,049***	0.544	1,078*	0.285	4,465	0.0021	0.0226***	0.0218*
Run · group	3	3,682	0.832*	458	0.185	6,432	0.0846	0.0028	0.0161*
Run · day	3	2,731	0.368	328	1.293*	3,309	0.0643	0.0033*	0.0114
Run · exposure									
Total	3	1,188	0.328	134	0.924*	6,429	0.0607	0.0013	0.0032
Linear	1	1,884	0.739*	271	2.104*	1,665	0.1656*	0.0022	0.0020
Deviation from linearity	2	841	0.122	66	0.334	8,811	0.0082	0.0008	0.0037
Run · day · group	6	738	0.115	38	0.380	29,157***	0.0559*	0.0008	0.0017
Error 3	48	1,339	0.206	261	0.328	6,386	0.0515	0.0011	0.0047
Error 3a	12	1,480	0.242	394	0.260	7,176	0.0418	0.0013	0.0066
Error 3b	36	1,292	0.194	216	0.350	6,122	0.0547	0.0010	0.0040
r ₁		0.92	0.67	0.85	0.68	0.92	0.89	0.94	0.84
r ₂		0.47	0.35	0.40	0.17	0.47	0.38	0.51	0.37
Transformation of data		None	Loga-rithm	None	Loga-rithm	None	Loga-rithm	Square root	Square root

*** ~ $p < 0.1\%$, ** ~ $p < 1\%$, * ~ $p < 5\%$, ° ~ $5\% < p < 10\%$.

well-controlled conditions and without any simultaneously occurring gaseous and particulate pollutants. Spectroscopy grade toluene was used to enable the exclusion of additive or synergistic effects due to impurities. The exposure in the workplace to technical grade toluene containing more impurities than spectroscopy grade toluene, to peak concentrations, to simultaneously occurring other gaseous and particulate pollutants, to high local temperatures, noise, etc, however, makes it probable that less adverse effects are caused by the present exposure than by exposure to a similar average concentration of toluene in the workplace.

We were not able to detect any absorption of toluene during the passage of inspiration air through the nose, which is in accordance with the low solubility of toluene in water and with its low reactivity.

Only slight irritation was reported for the mucous membranes of the eyes and the airways, and even at 100 ppm six subjects did not report any irritation. The highest average irritation and the highest individual irritation experienced were 13

and 64, respectively, on a scale with 100 (strong irritation) as the end point. Inter-individual variation in irritation was thus

Table 6. Results of seven performance tests after 5-h exposure to clean air. (ROC = receiver operating characteristic).

Performance tests	Arithmetic mean	Standard error of the mean
Rotary pursuit % contact time	53.0	4.5
Screw plate Time (s)	417	25
Landolt's rings Time (s)	56.1	5.9
Errors/100 rings	0.25	0.25
Bourdon Wiersma Time (s)	106	27
Errors/175 figures	1.31	0.38
Multiplication Time (s)	792	48
Errors/25 units	3.50	0.66
Sentence comprehension Time (s)	339	18.7
Errors/100 statements	2.13	0.52
Word memory Area under ROC (= score)	0.771	0.035
Beta (= criterion)	0.959	0.202

Table 7. Results of the analysis of variance on the test data from eight performance tests. (RP = rotary pursuit, MT = multiplication time, ME = multiplication errors, LR = Landolt's rings, BWT = Bourdon Wiersma time, BWE = Bourdon Wiersma errors, SP = screw plate, WMA = word memory area, WMB = word memory beta, r = correlation coefficient).

Source of variation	Degrees of freedom	RP (s ²)	MT (10 ² · s ²)	ME (s ²)	LR (10 ² · s ²)	BWT (10 ² · s ²)	BWE (s ²)	SP (10 ² · s ²)	WMA (10 ² · s ²)	WMB (s ²)
Group	3	3010	85.0*	73.45	105.7	58.15*	9.26	66.8	2.54	1.38
Error 1	12	1345	22.9	63.5	65.2	13.15	26.94	20.0	6.76	0.91
Day	3	3512***	58.8***	18.59*	37.8***	12.1***	31.05**	26.3***	0.50	0.386
Exposure										
Total	3	0.37	0.18	10.89	1.73	0.16	6.18	1.28	0.14	0.144
Linear	1	1.01	0.01	21.25*	3.39*	0.46	5.20	2.52*	0.18	0.306
Deviation from linearity	2	0.05	0.26	5.70	0.90	0.00	6.67	0.68	0.13	0.062
Group · day	6	27.9	0.10	5.44	0.80	0.36	5.54	0.46	0.22	0.435
Error 2	36	26.9	0.86	5.64	0.88	0.82	4.83	0.77	0.92	0.387
Run	1	975***	16.94***	17.26*	11.66***	2.00*	12.5	5.17***	7.20***	0.098
Run · group	3	13.3	1.02	2.22	0.62	0.20	5.77	0.84*	0.03	0.232
Run · day	3	19.0	0.06	1.96	1.24	0.08	2.36	0.74	0.28	0.066
Run · exposure										
Total	3	4.82	0.14	8.38	0.40	0.09	3.40	0.32	0.12	0.298
Linear	1	7.60	0.23	4.66	0.21	0.12	8.43	0.08	0.04	0.015
Deviation from linearity	2	3.42	0.10	10.24*	0.50	0.06	0.88	0.44	0.16	0.440
Run · day · group	6	34.4**	0.72	3.03	0.75	0.46	3.08	0.24	0.21	0.185
Error 3	48	10.20	0.53	3.26	0.65	0.31	3.87	0.28	0.21	0.216
Error 3a	12	14.05	0.57	2.48	0.85	0.36	4.74	0.26	0.32	0.115
Error 3b	36	8.95	0.51	3.52	0.58	0.29	3.57	0.29	0.18	0.253
r ₁		0.94	0.85	0.72	0.93	0.85	0.46	0.90	0.84	0.41
r ₂		0.45	0.24	0.27	0.15	0.45	0.11	0.47	0.63	0.28
Transformation of data		None	Logarithm	None	Logarithm	Logarithm	None	Logarithm	None	Logarithm

*** ~ p < 0.1 %, ** ~ p < 1 %, * ~ p < 5 %, ° ~ 5 % < p < 10 %.

very big.

The sensitivity of the eyes and the nose were identical and constant during the exposure day. There was no adaptation in the irritation response. There was less irritation of the throat and lower airways than of the eyes and the nose, and the dose effect at the two first-mentioned positions was not statistically significant. The mucociliary flow in the nose was not influenced, and there was no change in nasal resistance to breathing or in the resistance of the lower airways. This finding indicates that no engorgement of the mucous membranes or increase in mucus production took place. These effects are prominent when irritating substances such as sulfur dioxide are inhaled (6).

In reviews of toluene toxicity (12, 20, 27) several studies are listed concerning the irritative effects of toluene. The evidence is ambiguous, however. From the present study it appears that, in concentrations up to the present hygienic standard of 100 ppm, pure toluene is only slightly irritating for the mucous membranes. On the other hand the odor sensation was strong and was felt to be unacceptable by 20 % of the subjects exposed to 100 ppm. This result is in accordance with the odor thresholds stated in the literature. During the last decade the range reported has been from 0.2 to 16 ppm (16).

At the end of the exposure period about 29 % of the inhaled toluene was present in the end expiratory air, indicating an absorption of about 71 %. This finding is also in accordance with other observations. Åstrand (1) thus found that the alveolar concentration reached the steady state in 15 subjects exposed under controlled conditions to 100 ppm of toluene for 30 min. During rest the alveolar concentration was 20 %, and during work (50 W) it was 35 %, of the inhaled value. In an investigation of toluene exposure in a photogravure printing plant the toluene content in alveolar air was about 20–50 % of the mean concentration in the inspiratory air at the same time (22).

Our performance test battery was composed to cover visual perception, motor performance, the coordination between visual perception and motor performance, vigilance, and intellectual capacity. These functions are all very important for most workers exposed to toluene, eg, painters

and workers in the printing industry. There were no significant changes in any tests due to the toluene exposure, but we saw some minor, nonsignificant changes in performance due to the day-long toluene exposures. These changes might indicate a slight neurotoxic effect.

Although the objective behavioral changes were small, the subjects felt the work to be more strenuous and their reaction time prolonged during the 100-ppm exposure in comparison with the other exposures. In fact the measured reaction times showed no effect of the 6-h toluene exposure, a finding also reported by Ogata et al (23). This result indicates that an increased effort was necessary at this exposure condition to obtain an unaltered test result.

Another indication of a slight neurotoxic effect of toluene exposure is the significant increase that occurred for headaches, dizziness, and feeling of intoxication only during the 100-ppm exposure. In the literature (21) moderate fatigue and slight headache have been reported by one of three volunteers exposed to 100 ppm of toluene during 8 h, and drowsiness and very mild headache occurred in one of two volunteers exposed to 50 ppm during the same period of time. The present hygienic standard in the United States and in Denmark is 100 ppm (3, 8), but in Denmark a change to 50 ppm has been proposed. From this study of the acute exposure of young healthy males it is apparent that workday-long exposure to 100 ppm causes no change in airway physiology and only minor changes in performance, but it causes discomfort for more than "the small percentage of workers" which is the basis for the setting of hygienic standards (3, 8). During exposures to 10 or 40 ppm this discomfort was not experienced; therefore a hygienic standard of 40 ppm of toluene would be adequate to fulfill the previously mentioned goal. A hygienic standard of that magnitude would also protect the workers against the greater irritation caused by the excursions to concentrations of up to 1.5 of the hygienic standard which are allowed for 15-min periods provided the daily average is not above the hygienic standard (8). The final setting of a health-based hygienic standard for toluene should also include experiences from short-term exposures at different

work loads for workers with daily exposure to toluene and from long-term exposures in the workplace.

The introduction of energy efficient procedures due to the high cost of energy has caused a decrease in the supply of ventilating air and an increase in the use of recirculation air. It has been suggested that the concentration of any contaminant in supply air should never exceed 10 % of the hygienic standard (4). From the present study it appears that toluene reduces the perceived quality of the air (fig 4) and that it is moderately odorous. A supply of air with 10 ppm of toluene would cause an initial impression of a decrease in air quality and a slight perception of odor, but both effects would disappear after 1 to 2 h of continuous exposure.

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References

1. Åstrand I. Uptake of solvents in the blood and tissues of man. *Scand j work environ health* 4 (1975) 199–218.
2. Alvey NG, Banfield CF, Baxter RI, Gower JC, Krzanowski WJ, Lane PW, Leech PK, Nelder JA, Payne RW, Phelps KM, Rogers CE, Ross GJS, Simpson HR, Todd AD, Wedderburn RWM, Wilkinson GN. GENSTAT: A general statistical program. Rothamsted Experimental Station, Rothamsted (England) 1977.
3. American Conference of Governmental Industrial Hygienists. TLV. Cincinnati, OH 1982.
4. American Society of Heating, Refrigerating and Airconditioning Engineers. ASHRAE standard for ventilation required for acceptable air quality 62–81. Atlanta, GA 1981.
5. Andersen I, Camner P, Jensen PL, Philipson K, Proctor DF. Nasal clearance in monozygotic twins. *Am rev respir dis* 110 (1974) 301–305.
6. Andersen I, Lundqvist GR, Jensen PL, Proctor DF. Human response to controlled levels of sulfur dioxide. *Arch environ health* 28 (1974) 31–39.
7. Andersen I, Lundqvist GR, Proctor DF, Swift D. Human response to controlled levels of dust. *Am rev respir dis* 119 (1979) 619–627.
8. Arbejdstilsynet. Liste over hygiejniske grænseværdier. Copenhagen 1981.
9. Baddeley AD. A 3-min reasoning test based on grammatical reasoning. *Psychon sci* 10 (1968) 341–342.
10. Baddeley AD, Figueredo JW de, Hawkswell Curtis JW, Williams AN. Nitrogen narcosis and performance under water. *Ergonomics* 11 (1968) 157–164.
11. Cochran WG, Cox GM. Experimental designs. J Wiley and Sons Inc, New York, NY 1957.
12. Cohr KH, Stokholm J. Toluene: A toxicologic review. *Scand j work environ health* 5 (1979) 71–90.
13. Dubois AB, Botelho SY, Bedell GN, Marshall R, Comroe JH. A rapid plethysmographic method for measuring thoracic gas volume, a comparison with a nitrogen washout method for measuring FRC in normal subjects. *J clin invest* 35 (1956) 322–326.
14. Dubois AB, Botelho SY, Comroe JH. A new method for measuring airway resistance in man using a body plethysmograph, values in normal subjects and in patients with respiratory disease. *J clin invest* 35 (1956) 327–335.
15. Gamberale F, Hultengren M. Toluene exposure: II Psychophysiological functions. *Work environ health* 9 (1972) 131–139.
16. Gemert LJ van, Nettenbreijer AH. Compilation of odour threshold values in air and water. Central Institute for Nutrition and Food Research TNO, Zeist 1977.
17. Hänninen H, Lindström K. Behavioral test-battery for toxicopsychological studies. Institute of Occupational Health, Helsinki 1979.
18. Kay H. Report on arctic trials on board HMS Vengeance February–March 1949. Medical Research Council, London 1949. (Royal Naval Personnel Research Committee report no 534).
19. Löfberg HA, Löfstedt B, Nilsson I, Wyon DP. Combined temperature and lighting effects on the performance of repetitive tasks with differing visual content. National Swedish Institute for Building Research, Gävle 1975. (SIB bulletin 16).
20. National Institute for Occupational Safety and Health. Occupational exposure to toluene, Washington, DC 1973.
21. Oettingen WF von. The toxicity and potential dangers of toluene. *J am med assoc* 118 (1942) 579–584.
22. Övrup P, Hultengren M, Lindqvist T. Exposure to toluene in a photogravure printing plant. *Scand j work environ health* 4 (1978) 237–245.
23. Ogata M, Tomokuni K, Takatsuka Y. Urinary excretion of hippuric acid and m- or p-methylhippuric acid in the urine of persons exposed to vapours of toluene and m- or p-xylene as a test of exposure. *Br j ind med* 27 (1970) 43–50.
24. Poulton EC. Environment and human efficiency. Charles C Thomas, Springfield, IL 1970.
25. Suzuki H. Autonomic nervous responses to experimental toluene exposures in humans. *Jpn j ind health* 15 (1973) 379–384.
26. Teichner WH, Wehrhamp RF. Visual motor performance as a function of short duration ambient temperature. *J exp psychol* 47 (1954) 447–450.

27. WHO Study Group. Recommended health-based limits in occupational exposure to selected organic solvents. World Health Organization, Geneva 1973. (WHO techn rep series 664).
28. Wyon D, Andersen I, Lundqvist GR. The effects of moderate heat stress on mental performance. Scand j work environ health 5 (1979) 352–361.
29. Wyon DP, Lewis MI, Kok R, Meese GB. The effects of moderate cold and heat stress on the potential work performance of industrial workers: Part 1. Background and experimental procedures. National Building Research Institute, Pretoria 1980. (CSIR research report 381).

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