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Effects of Toluene Exposure on the Spontaneous Cortical Activity in Rats

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GHOSH, T. K., R. L. COPELAND, JR., J. C. GEAR AND S. N. PRADHAN. *Effects of toluene exposure on the spontaneous cortical activity in rats*. PHARMACOL BIOCHEM BEHAV **32**(4) 987–992, 1989.—Effects of toluene on the electroencephalogram (EEG) and its power spectra were measured during a 2-hr exposure in a dynamic inhalational chamber in rats. Rats were exposed to one of six graded concentrations (110.6, 162.5, 432, 676, 1558, 2730 ppm) of toluene on different days. It was found that the duration of waking (W) was increased with a decrease in duration of rapid eye movement (REM) sleep even at 110.6 ppm. Duration of nonrapid eye movement (NREM) sleep was decreased with an increase of W and a decrease of REM sleep at 162.5 ppm. Dose-related effects were noted in higher concentrations. The power of δ frequency band was increased with a decrease of θ frequency band power at hr 1 of exposure to 676 ppm during REM sleep recorded from the visual cortex. The power of θ frequency band was also decreased at hr 2 of exposure at 432 ppm. During W and NREM sleep power spectra were not changed significantly. Results indicate that the changes of EEG are a sensitive measure of the effects of toluene on the central nervous system (CNS).

Toluene EEG Power spectrum analysis Inhalation

TOLUENE, as a pure solvent or as a component of the mixture of industrial solvents, is a cause of health hazard in the industry (5, 6, 11, 19, 25). In addition, it has been reported that inhalation of commercial products containing toluene by solvent abusers produces central and peripheral nervous system degenerations and injuries to kidney and liver (10, 13, 19). Laboratory animals have been exposed to toluene to delineate its toxicological properties. As a lipophilic substance, toluene is accumulated in the brain and produces effects on central nervous system (CNS) functions. For this reason, the effect of toluene on the CNS has been investigated directly or on some of its functions, e.g., behavior (6). It was observed that the operant behavior in animals is affected at a minimal concentration of the solvent which does not cause pathological changes, and effects of toluene on different operant behaviors have been reported by several investigators (12, 15, 17, 23).

The electroencephalogram (EEG), as a fundamental neurophysiological process, has been used in neurotoxicological studies (7). A few studies have been conducted to measure the EEG changes during toluene exposure in laboratory animals (14, 22, 30, 32). In these studies, EEG and EMG recordings were used for assessments of sleep-waking stages and frequency analysis of EEG waves were made for further quantitation. Moreover, high concentrations of toluene were employed in rats (1000–40,000 ppm) and cats (12,000–52,000 ppm) in these experiments. However, some quantitative method such as the power spectrum analysis (36,37) has not been utilized for neurotoxicological investigations of toluene.

A transient decrease of the reinforcement rate in a behavioral schedule was observed at hr 1 of exposure to low concentrations of toluene (142, 211, 495 ppm) in our experiments in rats (16). In an attempt to correlate such behavioral effects of toluene to its electrophysiological effects, in the present study the EEG spectral power was measured in rats exposed to low concentrations of toluene.

METHOD

Animal

Eight male F344 rats obtained from Charles River Breeding Lab were used in this study. They weighed 180–200 g at the time of surgical operation. Rats were housed individually in stainless steel cages in the animal room with a 12-hr light-darkness cycle (light: 7 a.m. to 7 p.m.). The animal care room was maintained at a temperature of 24 ± 1°C and a relative humidity of 55 ± 5%.

Surgical Procedure

Implantation of electrodes (consisting of 0-80 × ⅛ inch stainless steel screws, Plastic Products Co.) was carried out under sodium pentobarbital anesthesia (40 mg/kg, IP). Two electrodes were implanted over the visual cortex (6.0 mm posterior to the bregma, and 3.5 mm lateral to the midline on both sides). Two other electrodes were placed over the somatosensory cortex (1.5

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mm posterior to the bregma, and 3.0 mm lateral to the midline on both sides). Another electrode placed 11 mm anterior to the bregma on the midline served as the ground. For electromyogram (EMG) recording, pairs of stainless steel wires were inserted into the neck muscles. All electrodes were soldered to a miniature socket (March Electronics, MMS22-7) which was attached to the skull with dental cement.

Polygraphic Recordings and Classification of Sleep-Waking Stages

Two weeks following the surgery, each rat was placed in the inhalational chamber (see later) for one week of habituation, while EEG and EMG were recorded via a Grass Model 7 Polygraph for 6 hr daily (9:30 a.m. to 3:30 p.m.). EEG frequencies from 0.3 to 30 Hz and EMG frequencies from 5 to 75 Hz were allowed to pass through the filter. The EEG from the visual cortex was recorded via two electrodes placed on the opposite sides of the visual cortex. Similarly, the electrodes on two sides of the somatosensory cortex were used to record EEG in another channel. The EMG was recorded from the neck muscles. Even after initial habituation, when the animal was placed inside the inhalational chamber, it took some time for the sleep cycles to be stabilized. For this reason, only the last 4-hr recordings (11:30 a.m. to 3:30 p.m.) were used for calculating the durations of sleep-waking stages per hour. When these values from the last two consecutive days were consistent, rats were exposed to toluene for 2 hr (12:30 p.m. to 2:30 p.m.). One-hour recording preceding the exposure was considered as the preexposure control, and the postexposure effect was recorded during the last hour. Data from the day preceding the exposure were considered as the previous day control.

Polygraphic recordings of the rat were grouped into three stages, as described by others (4,8): 1) waking (W) characterized by the low amplitude EEG from both the somatosensory and visual cortices and the high amplitude EMG; 2) nonrapid eye movement (NREM) sleep characterized by the high amplitude irregular EEG from both the cortices and the low amplitude EMG; 3) rapid eye movement (REM) or paradoxical sleep (PS) characterized by the low amplitude EEG from the somatosensory cortex, continuous θ waves in the visual cortex and the low amplitude EMG. The θ activity originating from the electrode over the visual cortex during REM sleep was confirmed with spectral analysis.

Power Spectrum Analysis

EEG and EMG activities were also recorded on an FM magnetic tape recorder (A. R. Vetter Co., Model C4). Power spectral analysis of EEG was performed offline using a Nicolet MED-80 minicomputer system which uses Fast Fourier Transformation for computation. EEG power spectra were derived from 10-sec samples of EEG that were digitized at a sampling rate of 50/sec and power spectral densities were estimated from 0 to 25 Hz and plotted on a X-Y plotter. The digital values of power spectra of the four major frequency bands, δ (0–4 Hz), θ (4–8 Hz), α (8–13 Hz) and β (13–20 Hz) from six to twelve 10-sec EEG samples (for details see the Statistical Analysis section) during each of W, NREM and REM sleep stages were obtained from the printout.

Exposure to Toluene

Rats were exposed to toluene (laboratory grade, Fisher Scientific Company) in a dynamic inhalational chamber described in detail by Pradhan and Copeland (27). Briefly, the chamber consisted of an inverted cylindrical glass chromatography jar suitable for exposure of a single rat. The chamber was infused with a flow of air derived from the house air supply. After filtering the air, it was passed through a pressure regulator and a gas flowmeter. Toluene was injected into an evaporating flask by an infusion pump. The filtered house air was mixed with toluene vapor in the flask and passed through a condenser to lower the temperature of the mixture before entering into the exposure chamber. To obtain a homogeneous distribution of vapor into the chamber the mixture was introduced through a cross-shaped copper tubing system suspended from the ceiling of the chamber.

While the exposure was continued, the concentration of toluene in the chamber was monitored by collecting gas samples in a sampling bulb from inside the chamber at 15-min intervals and then injecting 1 ml of the sample into a Shimadzu dual-column gas chromatograph (GC) equipped with flame ionization detectors (Model GC Mini 2). The concentration was measured with the help of a digital integrator connected to the GC. The average concentration of toluene within a day based on the samples was calculated as the mean and variation of session means within a concentration was expressed as the grand mean ± S.E. Silanized glass columns (3.5 meter, 3 mm i.d.) were packed with GP 5% SP-1200/5% Bentone 34 on 100/120 Supelcoport. Gas flow for the GC was maintained at N_2 500 ml/min, air 450 ml/min, and H_2 40 ml/min. Column temperature was maintained at 80°C and the injector and detector temperatures were 110°C.

Rats were exposed to one of the six concentrations of toluene (e.g., 110.6 ± 5.0, 162.5 ± 15.4, 432 ± 17, 676 ± 34, 1558 ± 52.3, 2731 ± 79.5 ppm) for 2 hr in a random order on different days. One rat was not exposed to more than four concentrations and to prevent the effects of repeated toluene exposure, the same rat was not exposed to the next concentration for at least 15 days. Thus, for each concentration, 6 rats were exposed.

Statistical Analysis

The behavioral stage duration variables (awake, REM sleep, NREM sleep) were analyzed by taking the difference between the exposure day value and the previous day control value during each hour, for each animal. These differences were analyzed with a cell means model in the general linear models procedure in SAS, so that the exposure/control comparison is modeled directly, yielding a single degree-of-freedom test of significance ($p<0.05$) for each exposure by time cell.

In order to analyze the spectral power variables, the control value for each animal was determined at each exposure level and stage by taking the mean of twelve 10-sec samples of EEG during the preexposure control period (one hour before the exposure) and twelve 10-sec samples during various times on the previous day. Power spectra of six 10-sec samples of each stage during the last halves of the first and second hours of the exposure period, and the last half of the first hour of the postexposure period, were calculated for each of the spectral power variables, at each exposure level and stage. So separate, independent analyses were performed for each variable (i.e., each frequency band from a particular area of cortex) in each behavioral stage and at each exposure level. In each analysis, paired *t*-tests were used to compare the control value to the first and second exposure hour and the postexposure hour. These pairwise comparisons were considered significant, using the Bonferroni correction for the three multiple comparisons within each analysis, at $p<0.05$.

RESULTS

Duration of Sleep-Waking Stages

Measurement of hourly durations of W, NREM sleep and PS

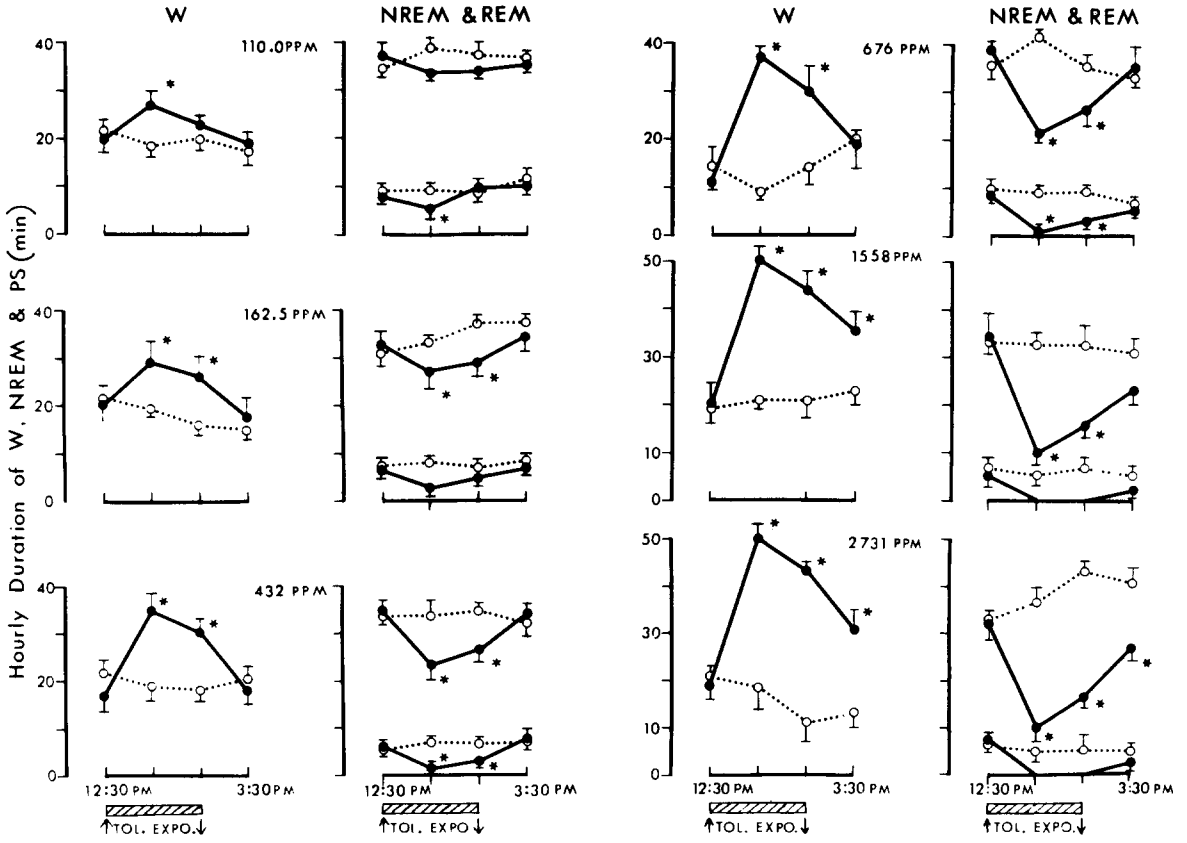

FIG. 1. Changes in the hourly durations of waking (W), nonrapid eye movement (NREM) sleep and rapid eye movement (REM) sleep during exposure to toluene. Durations of each time period are compared between the previous day control (dotted lines with open circles) and exposure day (solid lines with closed circles). The circles and vertical bars represent mean and S.E. of hourly data (from 6 rats). Toluene exposure (Tol. Expo.) was continued from 12:30 p.m. to 2:30 p.m. and postexposure effect was measured from 2:30 p.m. to 3:30 p.m. *$p<0.05$.

during control days showed that NREM sleep dominated during the 4-hr recording time (Fig. 1). This baseline pattern was changed during exposure to toluene at the minimal level of 110.6 ppm. At this concentration an increase in W and a decrease in REM sleep were noted during hr 1 of exposure. However, hourly duration of these stages returned to the control level during hr 2 of exposure. At 162.5 ppm the increase in W with a decrease in NREM sleep were noted during hr 1 and hr 2 of exposure. REM sleep during the hr 1 of exposure at 162.5 ppm was also decreased. Hourly duration of these three stages returned to the control level during the postexposure period. During exposure to 432, 676, 1558 and 2731 ppm of toluene, the changes noted at 162.5 ppm were more prominent and even extended to the postexposure period at higher concentrations (Fig. 1). The decrease in REM sleep noted at hr 1 of exposure was extended to hr 2 at higher concentrations; at 1558 and 2731 ppm REM sleep was absent during the exposure period. The increase in W during exposure to 1558 and 2731 ppm persisted during the postexposure period. NREM sleep remained decreased during the postexposure period at 2731 ppm (Fig. 1). The change of the duration ofW from the previous day control at hr 1 of the exposure period showed a gradual increase with the increase of toluene concentrations. A gradual decrease of durations of NREM and REM sleep was also noted, as the toluene concentration was increased (Fig. 2).

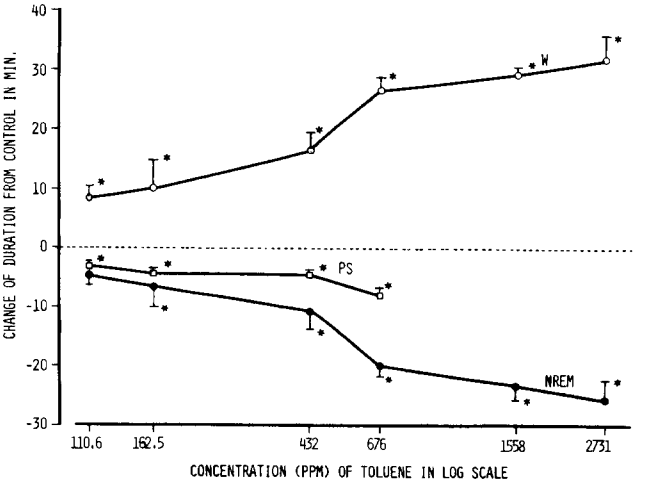

FIG. 2. Dose-related changes in the hourly durations of W, NREM and REM sleep during hr 1 of exposure to toluene. The circles/squares and vertical bars represent mean and S.E. of the difference between hr 1 durations for the previous (control) day and the exposure day (6 rats). Toluene concentration in ppm in log scale on the x-axis. REM sleep was absent at 1558 and 2731 ppm of toluene. *$p<0.05$.

TABLE 1

POWER SPECTRUM ANALYSIS OF EEG RECORDED FROM TWO CEREBRAL CORTICAL AREAS DURING DIFFERENT SLEEP-WAKING STAGES IN CONTROL CONDITION

Cortical area	Sleep-Waking Stages	Power (picowatts)* δ(0–4 Hz)	θ(4–8 Hz)	α(8–13 Hz)	β(13–20 Hz)
Visual cortex	W	2469 ± 242	2913 ± 474	490 ± 66	217 ± 46
	NREM	6742 ± 284	5310 ± 306	2118 ± 144	476 ± 38
	REM	1999 ± 123	10006 ± 513	1936 ± 154	290 ± 14
Somatosensory cortex	W	651 ± 63	594 ± 63	230 ± 35	136 ± 27
	NREM	2545 ± 335	2644 ± 148	1540 ± 78	697 ± 46
	REM	736 ± 42	886 ± 63	324 ± 25	139 ± 10

*Mean ± S.E. of data from 6 animals; twenty-four 10-sec EEG samples were taken from each animal; W, waking; NREM, nonrapid eye movement sleep; REM, rapid eye movement sleep.

Power Spectrum Analysis

Power spectra of EEG samples recorded from somatosensory and visual cortices during sleep-waking stages indicate some qualitative and quantitative differences during W, NREM and REM sleep. The spectral power derived from the visual cortex was higher compared to that of the somatosensory cortex during all the stages. The W was associated with less power compared to that of NREM sleep and power was higher at δ and θ frequency bands in both the cortices. In NREM sleep predominant power was noted from both the cortices at δ and θ frequency bands and then gradually diminished in 13–20 Hz range. REM sleep was associated with predominent θ frequency band power at the visual

TABLE 2

EFFECT OF TOLUENE EXPOSURE ON THE POWER SPECTRUM ANALYSIS OF EEG RECORDED FROM VISUAL CORTEX DURING REM SLEEP

Concentration (ppm)	Condition	Power (picowatts)* δ(0–4 Hz)	θ(4–8 Hz)	α(8–13 Hz)	β(13–20 Hz)
110.6 ± 5.0	Control	1999 ± 123	10,006 ± 513	1936 ± 154	290 ± 14
	Hr 1 exposure	2285 ± 338	9842 ± 1554	2581 ± 395	275 ± 30
	Hr 2 exposure	2381 ± 531	9759 ± 917	1878 ± 307	313 ± 33
	Postexposure	2000 ± 342	10,047 ± 818	1994 ± 371	313 ± 44
162.5 ± 15.4	Control	2273 ± 150	10,815 ± 579	2112 ± 197	302 ± 17
	Hr 1 exposure	3227 ± 377	9185 ± 955	2540 ± 460	295 ± 38
	Hr 2 exposure	2618 ± 512	8746 ± 866	1790 ± 605	290 ± 32
	Postexposure	2603 ± 320	9745 ± 1047	1610 ± 296	316 ± 52
432 ± 17	Control	1845 ± 173	8515 ± 432	2177 ± 204	318 ± 31
	Hr 1 exposure	3961 ± 1663	7295 ± 1247	1769 ± 404	265 ± 31
	Hr 2 exposure	2265 ± 621	7091 ± 934†	2249 ± 405	296 ± 41
	Postexposure	1555 ± 234	8727 ± 801	1820 ± 188	384 ± 91
676 ± 34	Control	1439 ± 108	10,845 ± 549	1903 ± 176	261 ± 12
	Hr 1 exposure	2539 ± 357†	6499 ± 595†	1567 ± 294	236 ± 16
	Hr 2 exposure	2016 ± 405	8331 ± 950	2009 ± 398	284 ± 46
	Postexposure	1413 ± 193	10,187 ± 1157	2250 ± 469	289 ± 30
1558 ± 52.3	Control	1860 ± 76	9235 ± 823	1768 ± 301	331 ± 33
	Hr 1 exposure	—	—	—	—
	Hr 2 exposure	—	—	—	—
	Postexposure	1959 ± 537	8364 ± 756	2390 ± 663	397 ± 63
2731 ± 79.5	Control	1866 ± 290	8635 ± 770	1949 ± 292	266 ± 25
	Hr 1 exposure	—	—	—	—
	Hr 2 exposure	—	—	—	—
	Postexposure	1699 ± 593	8209 ± 649	1865 ± 677	315 ± 53

*Mean ± S.E. of data from 6 animals/concentrations (total n = 8).

†$p<0.05$ (paired t-test was performed between control and exposure hr with Bonferroni correction; for further details of statistical analysis see text).

cortex. The powers of other frequency bands in REM sleep were lower compared to that of NREM sleep like W stage. In the somatosensory cortex during REM sleep all the frequency bands showed less power compared to those in NREM sleep, but the θ activity was not prominent like that of the visual cortex. Hence W and REM sleep cannot be distinguished from power spectral analysis of the somatosensory cortex (Table 1).

Power spectra were not changed significantly during REM sleep in EEG recorded from the visual cortex during exposures to 110.6 and 162.5 ppm of toluene. However, at 432 ppm significant decrease of θ power from control was noted at hr 2 of exposure. This decrease of θ power was noted with a significant increase of δ power at hr 1 of exposure to 676 ppm (Table 2). REM sleep was absent during exposure to 1558 and 2731 ppm. At these concentrations powers remained unchanged during postexposure period. Power spectra of α and β frequency bands in PS were not changed significantly during exposure and postexposure periods at all concentrations. REM sleep recorded from the somatosensory cortex also did not show any significant change.

Power spectrum analysis of EEG recorded during W and NREM sleep from somatosensory and visual cortices in rats exposed to toluene did not show any significant change.

DISCUSSION

Various neurological and psychotic symptoms have been observed in toluene abusers or in industrially exposed individuals (5, 6, 19). These symptoms include headache, dizziness, somnolence, fatigue, nausea, exhilaration and excitement, disturbance of sleep and insomnia (9, 18, 21, 28, 31, 33, 34). Laboratory animals also showed symptoms of excitation, restlessness, visual searching, scratching and turning (14,20). Changes of sleep-waking stages after toluene treatment have been investigated in rats (3,30). Sleep disturbance was reported during 4-hr exposure to 1000, 2000 and 4000 ppm of toluene in rats (30). The sleep stage was significantly reduced, while waking stage was significantly increased during exposure to 2000 and 4000 ppm. In the present study, an increase in W stage was observed even at 110.6 ppm. Changes observed at lower concentration may be due to the different methods of calculating percent change of an individual stage. While Takeuchi and Hisanaga (30) considered time duration of each stage per 6 hr (4-hr exposure plus 2-hr postexposure), in the present study hourly durations were measured. Increase in waking immediately after toluene injection (200, 400 and 600 mg/kg, IP) was reported in the bihourly measured data in rats (3). Behavioral excitation and EEG arousal were manifested after toluene exposure in cats (1, 14, 29) and rabbits (2).

A decrease in REM sleep has been reported during exposure to 2000 and 4000 ppm of toluene, but no change in REM sleep was observed at 1000 ppm (30). But in the present study a decrease in REM sleep was noted even at 110.6 ppm. As the concentration was increased, the decrease in REM sleep became more prominent.

The pattern of power spectra noted in this study from the visual cortex during different behavioral stages is similar to that reported by Young *et al.* (36). Power of δ frequency band was increased transiently, but significantly at 676 ppm at hr 1 of exposure (probably due to arousing effects of toluene inhalation) along with a significant decrease of power of frequency band during REM sleep recorded from the visual cortex. The decrease of θ power was noted even at hr 2 of exposure to 432 ppm. These changes probably indicate a disturbed REM sleep and at higher concentrations (1558 and 2731 ppm) REM sleep was totally absent. The θ activity recorded from the visual cortex during REM sleep may be due to the propagation of this activity from the underlying hippocampus, because it has been reported that θ rhythm is present in the hippocampus only in voluntary motion or REM sleep in rats (35). Frequency of θ activity recorded from the hippocampus was found to be decreased during 4-hr exposure to 4000 ppm of toluene (30). Significant reduction of hippocampal θ wave frequency was also reported during chronic exposure to 500 ppm of toluene in rats (24). The present study shows that toluene can affect θ power during REM sleep at 432 ppm and δ power along with the power of θ at 676 ppm. It has been reported that EEG in humans showed an excess of slow waves (9,28) and θ activity (21) after a prolonged solvent exposure. However, the effect on EEG may not be comparable in rats and humans.

In the present study power spectra were not changed significantly during W and NREM sleep. Frequency analysis of EEG by others showed a reduced cortical α component at 2000 ppm during W and during slow-wave sleep at 1000 ppm δ, θ and α components were reduced (30).

The mechanism by which toluene produces the changes in the power spectra and sleep-waking stages can not be determined from the present study. The subcortical EEG was not recorded in this study, but other investigators reported that toluene exposure can affect the electrical activity of the reticular formation, amygdala and cingulate gyrus in the cat (1,14) and the hippocampus in rats (24,30). The increased W and changes in power spectra during REM sleep especially in θ activity in this study probably indicate that the reticular formation and limbic cortex might be involved.

The gradual increase of W with a gradual decrease of NREM and REM sleep during toluene exposure indicate its excitatory effects on the brain. The increase of δ power with a decrease of θ power during REM sleep probably also suggests such excitatory effect of toluene. A decrease of reinforcement rate in the fixed-ratio (FR) liquid-reinforced behavior was observed previously in rats during toluene exposure (16). This change of operant behavior may be due to a stimulatory effect of toluene, since some stimulatory drugs (e.g., amphetamine and nicotine) have been shown to decrease reinforcement rate in food or liquid-reinforced FR schedules (26). It appears that the concentrations showing changes in sleep-wake stages (110.6 ppm) and in operant behavior (142 ppm) are lower compared to that (432 ppm) required to produce changes in EEG power spectrum. Thus behavioral parameters appear to be more sensitive to toluene exposure than EEG power spectrum analysis.

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