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Acute Electrophysiologic Effects of Inhaled Toluene on Adult Male Long-Evans Rats

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REBERT, C. S., M. J. MATTEUCCI AND G. T. PRYOR. *Acute electrophysiologic effects of inhaled toluene on adult male Long-Evans rats.* PHARMACOL BIOCHEM BEHAV **33**(1) 157–165, 1989.—Experiments were carried out in Long-Evans rats to verify and extend previous findings about the effects of toluene on sensory-evoked potentials (EPs) of Fischer-344 rats. Inhalation exposures to 3000 and 8000 ppm in Long-Evans rats confirmed that toluene 1) transiently enhances certain components of somatosensory, flash- and click-evoked (brainstem) potentials, 2) increases the latencies and interwave times of brainstem auditory-evoked responses, 3) depresses late components of the flash EP, 4) induces high frequency oscillations in the visual cortex, and 5) produces both facilitatory and suppressant effects on EPs, dependent on exposure concentration and time. New results indicated that toluene 1) has similar effects on Long-Evans as it does on Fischer-344 rats, 2) increases EEG theta activity, 3) has minor effects on cortical auditory and pattern-reversal EPs (PREP), but suppresses the steady-state PREP, and 4) induces oscillations in the visual cortex, irrespective of the presence of flashes.

Toluene Solvent abuse EEG Sensory-evoked potentials Rats

TOLUENE is a constituent of a variety of easily obtainable commercial products, such as paint thinners, cleaning agents, and glues, and it has been implicated in the genesis of neurologic abnormalities experienced by individuals that inhale the vapors of toluene-containing substances (7,8). Pure toluene is also employed for its psychoactive effects (4). To characterize the acute neurologic consequences of inhaling high concentrations of toluene (500 to 16000 ppm—the TLV is 100 ppm), we recently examined sensory-evoked potentials (EPs) of Fischer-344 rats (15). Toluene caused concentration- and time-related changes in brainstem-evoked auditory responses (BAERs), flash EPs (FEPs), and somatosensory EPs (SEPs). Facilitatory effects on EPs included amplitude enhancement of late components of BAERs early components of FEPs, and all components of SEPs. Late components of FEPs were depressed. Similar results for FEPs and SEPs were obtained, respectively, by Dyer *et al.* (5) and Mattsson *et al.* (9). Our results also suggested differential sensitivities of several SEP components to depressant effects of toluene, and that toluene induces fast (about 30 Hz) oscillations in the FEP. These kinds of investigations provide a rather unique characterization of solvent effects on the nervous system, using measurement endpoints that can be obtained in almost any species. It should be possible, therefore, to determine similarities and differences among solvents and, perhaps, suggest the bases for their different psychoactive properties and potentials for long-term deleterious effects.

We studied pigmented Long-Evans rats in this experiment for several reasons. We have on occasion had difficulty obtaining reliable FEPs in some batches of Fischer-344 rats but not in Long-Evans rats. This occurred in the second of our first set of toluene experiments (15), precluding a confident interpretation of those results. We also considered it important to evaluate pattern reversal EPs (PREPs), as these are most widely used in human clinical evaluations, but we have not been able to obtain those from Fischer-344 rats (unpublished observations). However, they are readily obtained in the Long-Evans strain (13). Furthermore, Dyer *et al.* (5) suggested that toluene has no effect on PREPs in the rat.

Other aims of this study were to 1) more thoroughly examine oscillatory EEG activity that appeared in the FEPs of Fischer-344 rats, 2) examine the effects of toluene on the spectral composition of the spontaneous EEG and the EEG "driven" by repetitive stimulation with acoustic and visual stimuli (steady state EPs), and 3) study the temporal development of the SEP during a period of exposure twice as long as that used previously; our previous study suggested that there would be a reversal of toluene's facilitatory effects with prolonged exposure.

METHOD

General Method

Subjects and surgical preparation. Seven male Long-Evans

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rats weighing an average of 322 g were obtained from Simonsen Laboratories in Gilroy, CA. On arrival at SRI they were kept in 23 × 14 × 45 cm plastic cages (3/cage) housed in laminar flow racks. Food and water were available ad lib. Lights were on from 7:00 a.m. to 7:00 p.m. Surgical procedures were like those described before (12). Epidural stainless steel screws were placed in the cranium with respect to bregma, over visual (6.0 P, 3.5 R), somatosensory (2.0 P, 2.0 L) and cerebellar (10.0 P, midline) cortices, and a reference electrode was implanted in the nasal bone (10.0 A, midline). Wires were soldered to the screws prior to implant to preclude heat damage to the cortex (6). Hooks embedded in the acrylic head plug were used during testing to hold the head to a frame with small rubber bands to maintain proper orientation of the rat to the stimulus sources (Fig. 1).

Exposure to toluene. Mallinckrodt reagent-grade toluene (99.8% pure) was used, and two channels of a mass-flow controlled gas blending system (Linde Model FM4575) were adjusted to produce the desired exposure levels. On the basis of a previous study of several concentrations (15), we first examined the effects of 8000 ppm toluene. One channel gated compressed air through a 4-l container of toluene, the outflow of which was mixed with air from the other channel. The two gas streams were mixed in a 500-ml flask, and this outflow was routed through a 190-ml sampling bulb in the line just before entry into the rat exposure chamber. The sampling bulb provided a source of gas samples just before exit to the rat. The rat was restrained in the plastic restrainer described by Rebert (12) that was modified as shown in Fig. 1 to provide a head-only exposure to gases during electrophysiologic recording. Presence of the plastic did not alter flash or pattern reversal visual EPs examined in other investigations (17). Total gas flow was maintained at 2500 ml/min because flow rates higher than 3000 ml/min produced sufficient noise to partially mask auditory stimuli. Gas concentrations were sampled from the sampling bulb and the needle in front of the rat's nose (Fig. 1), and exposures were calibrated against standards by gas chromatography. Extensive preexperimental tests demonstrated a high degree of consistency of concentrations with flow rate selection on the mass-flow controller. However, because movement and respiratory activity of the rats could modify the exposure to some extent, samples were periodically obtained during the several phases of the exposures.

Electrophysiological tests. A battery of electrophysiological tests (TSBAT) and other individual test routines were used. TSBAT consisted of samples of the spontaneous EEG and sensory-evoked potentials elicited by clicks, light flashes, and alternating checkerboard patterns. Four channels were recorded—each electrode with respect to the reference, and between the visual and cerebellar leads. Some analyses of the spontaneous EEG involved all four channels, but only a single channel of EP data was evaluated for each stimulus type (somatosensory and auditory EPs from somatosensory cortex, visual EPs from visual cortex, and brainstem auditory EPs from the cerebellum).

Spontaneous EEG. Four consecutive 5-sec samples of EEG (500 data points) were obtained with a recording bandpass of 1 to 40 Hz.

Click-evoked brainstem auditory-evoked response (CBAER). This response was elicited by 100-μsec duration clicks, with alternating polarity, delivered through a tweeter (1.5 to 20 kHz) suspended 24 cm directly above the rat's head (adding 0.8 msec to component latencies). Intensity was about 70 dB above the level at which CBAERs are just discernible in rats (13,16). CBAER averages (10-msec epoch) were based on 1,000 clicks presented at 18.8/sec, using a recording bandpass of 400 Hz to 6 kHz.

Cortical auditory-evoked potential (CAEP). Clicks of 100-μsec duration were presented at a rate of 0.7/sec to elicit a CAEP. Intensity was about 85 dB above threshold. Averages were based on 75 400-msec epochs, using a recording bandpass of 1 to 100 Hz. A stimulus rate of 7.4/sec was used to elicit the steady-state response (1 to 40 Hz recording bandpass, 2-sec epoch).

Pattern-reversal-evoked potential (PREP). The PREP was elicited by a reversing checkerboard pattern on a 24 × 18 cm television monitor placed 8 cm in front of the rat. At that distance, checks in the center of the visual field subtended 14° at the 256-check instrument setting. Dark checks were 2.9 FL and light checks were 56.5 FL. Two reversal rates were used—1.3/sec to elicit the PREP (1 to 150 Hz recording bandpass; 500-msec epoch) and 9.0/sec to elicit the steady-state PREP (SSPREP: 1 to 50 Hz recording bandpass, 1-sec epoch). The numbers of reversals included in each average, respectively, were 150 and 75.

Flash-evoked potential (FEP). FEPs were elicited by a Grass PS-2 strobe lamp (intensity = 16) centered 20 cm above and 7 cm in front of the rat, angled toward the rat's face. FEP averages obtained during TSBAT (500-msec epoch) were based on 50 stimuli presented at 0.37/sec, using a recording bandpass of 1 to 55 Hz. Prior to the FEP test the chamber was dimly lit (14 FL). The light was extinguished 15 to 30 sec prior to obtaining the FEP and then turned on again following FEP and SSFEP acquisition (which took about 6 min to complete). Obtaining the FEP during the earliest phases of dark adaptation seemed to enhance the P2N2P3 component complex. Flashes were presented at 7.4/sec to elicit the SSFEP (2-sec epoch).

During additional sequential recordings to study FEP oscillations, a bandpass of 15 to 55 Hz was used, the gain was doubled, and the recording epoch was 2 sec rather than 500 msec (in order to more readily examine any decline in oscillatory activity during the recording epoch).

Somatosensory-evoked potential (SEP). SEPs were elicited by 20-μsec duration, 3 mA, cathodal constant-current square waves applied at a rate of 1.3/sec via needles inserted into the midventral aspect of the tail (cathode proximal). The recording bandpass was 5 to 250 Hz (200-msec epoch), and each average comprised 150 samples.

Data quantification and analysis. EEGs were quantified by spectral analysis. EPs were quantified in three ways: 1) by measuring peak amplitudes (peak-to-peak) and latencies; 2) integrating the waveforms or portions thereof; and 3) spectral analysis. Statistical comparisons were made with repeated measures ANOVAs and/or *t*-tests. Because we evaluated a large number of variables, actual probability levels for Type I errors are given for results where $p \leqq 0.05$.

Procedures

Sessions involving the test battery. The entire test battery was run just before exposure to toluene (8000 ppm) to obtain baseline measurements. Also, FEP oscillations (2-sec epoch, etc.) and SEPs were recorded just before the exposure, and then at 10-min intervals during exposure, with the last test beginning 40 min after exposures began. After 50 min of exposure TSTBAT was repeated; exposures were terminated after 60 min. FEP oscillations and SEPs were obtained at 10-min intervals over the course of the recovery period. TSTBAT was again administered after 60 min of recovery.

Repeated SEPs during exposure to 3000 ppm toluene. To clarify results obtained with the test battery, SEPs were recorded several days after the main experiment, once just before and repeatedly (every 3 min) during a 21-min exposure of six rats (one of the original seven had to be euthanatized due to an injury inflicted by another rat) to 3000 ppm toluene.

Additional studies of visual cortex oscillations. To determine if decay of the FEP oscillations during the sampled epochs was due

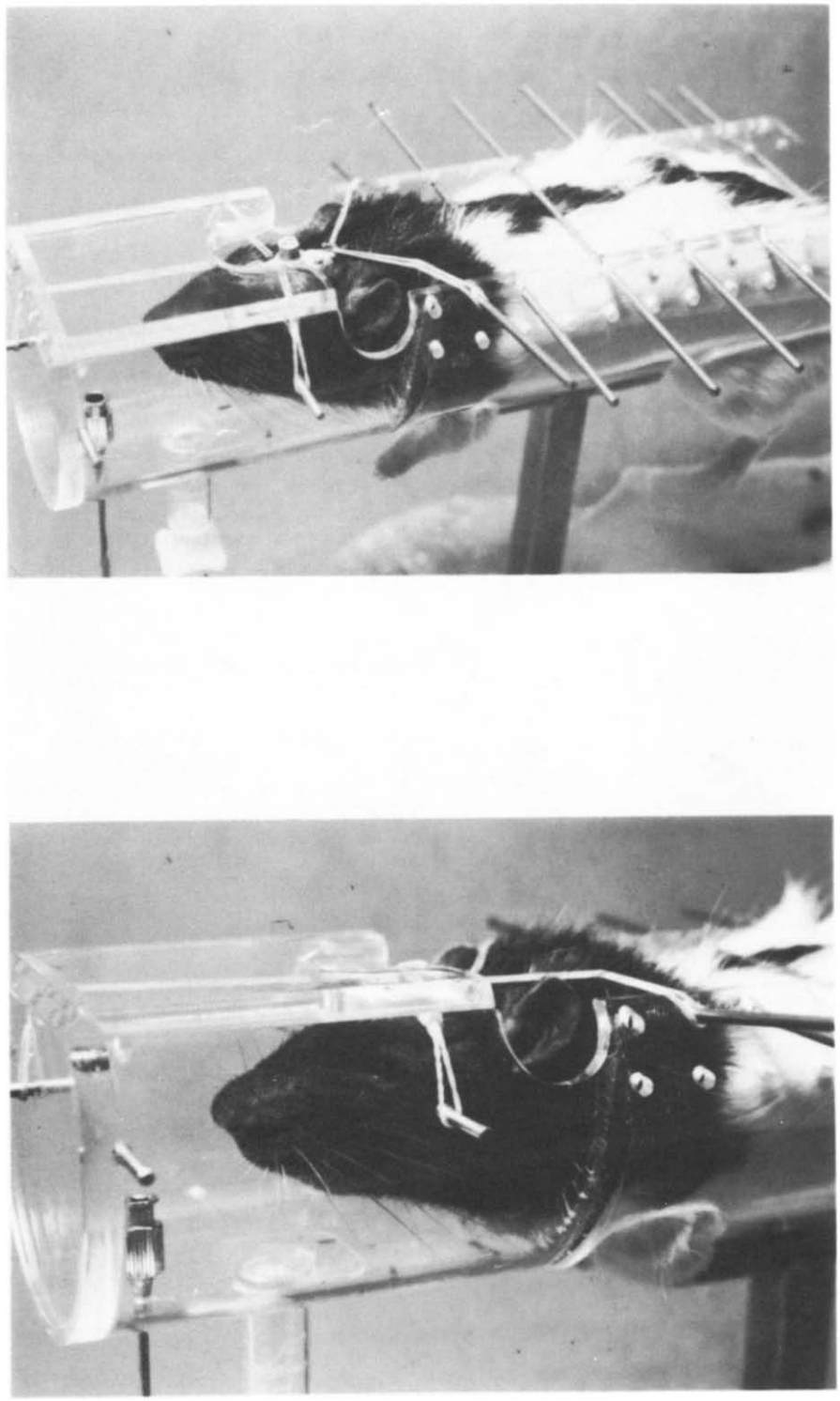

FIG. 1. Rat restrainer and head-only exposure system for electrophysiologic recording during exposure to volatile solvents [From (17).]

to actual decline in their amplitude, or a consequence of temporal "jitter" and loss of time-locking to the flash, 48 single, 10-sec epochs were recorded (15 to 55 Hz bandpass) before exposure and during the last 20 min of a 40-min exposure to 8000 ppm toluene, and 10 min after the end of exposure. Each single epoch was full-wave rectified and then digitally filtered with a low pass value of 2 Hz to smooth the rectified profile. The epochs were then averaged together. This procedure was done during two separate

sessions—during one, the epochs were obtained without the presence of flashes. Approximately 3 days separated the several exposures for an individual rat.

RESULTS

Exposure Level and Colonic Temperature

Actual level of exposure to the nominal concentration of 8000 ppm at the times that the test battery was run averaged 8567 ppm with standard error of 652 ppm. Changes in colonic temperature across conditions were inconsequential except for the BAER—average (SE) temperatures were 38.0 (0.1), 37.0 (0.3), and 38.0 (0.1)°C in the preexposure, exposure, and postexposure TSTBAT runs of the main experiment, respectively. Temperature changed gradually over the course of the main experiment, reaching 37°C after 50 min. The decrease in temperature during exposure could induce a latency increase in BAER components of about 70 μsec (18).

During the separate examination of 2-sec FEP epochs, exposures averaged 8550 (SE = 210) ppm and colonic temperatures were 37.6 (0.3), 37.3 (0.2), and 37.4 (0.2)°C before, during, and after exposure, respectively. During the examination of epochs with and without flashes present, exposures were, respectively, 8220 and 7767 ppm; mean colonic temperatures ranged from 37.1 to 37.4°C.

Spontaneous EEG

The spontaneous EEG recorded with respect to the reference in the nasal bone was sometimes contaminated by olfactory bulb oscillations associated with respiration. These oscillations occurred with a frequency of about 1.5 Hz during the preexposure recordings and increased up to 3.0 Hz during exposure. They were not apparent in recordings between visual and cerebellar cortex or in derived records reflecting activity between visual and somatosensory cortex. In some instances it appeared as if toluene suppressed olfactory bulb activity.

Toluene enhanced a spectral peak in the range of EEG theta activity (about 6.5 Hz). Peak power was 118 to 360% of the baseline value during exposure, varying among recording montages. The highest values were obtained in visual and somatosensory cortices recorded with respect to the reference electrode [tVIS(6) = 4.86, $p = 2.82 \times 10^{-3}$; tSOM(6) = 3.51, $p = 1.27 \times 10^{-2}$]. The smallest value was in the cerebellar-to-reference pair. The relative magnitudes of increased theta among all pairs of leads suggested that it was not due to activity at the reference electrode and that it occurred primarily in visual and somatosensory cortices. During the postexposure test, theta power was 73% and 49% of the value during exposure in visual and somatosensory cortices, respectively—still significantly different from the preexposure level for visual, $t(6) = 5.54$, $p = 1.46 \times 10^{-3}$, but not somatosensory cortex. This differential rate of recovery in these two regions also suggests independence of the phenomenon from activity at the reference electrode.

When 4-Hz EEG spectral bands were integrated, the changes across conditions were similar for the several recording sites, as exemplified in Fig. 2 (VIS/REF). Activity in the 0- to 4-Hz range decreased during exposure ($p = 2.0 \times 10^{-3}$), without much recovery during the postexposure test. In all other frequency bands, EEG power increased (significant only for frequencies above 12 Hz; $ps = 2.9 \times 10^{-3}$ to 7.5×10^{-3}) with essentially full recovery to normal after exposure.

Click-Evoked Potentials

Group-averaged BAERs obtained during runs of TSTBAT are shown in Fig. 3. In these records a small P2 component typically observed in Fischer-344 rats was not evident, and the "third" component was doubly-peaked [this has previously been observed (14)]. All of the individual peak latencies of the CBAER (P1 to P6) and the interwave times (P1–P3, P3–P5, P1–P5) were significantly prolonged by toluene; F-ratios (2,12) ranged from 6.04 to 76.7, $ps = 1.53 \times 10^{-2}$ to 1.5×10^{-7}. Significant changes in amplitude were restricted to middle and late components. The N3P4 component was reduced by 60%, $F(2,12) = 9.6$, $p = 3.21 \times 10^{-3}$, whereas components P4N4 and N4P5 increased by 8% and 77%, respectively ($ps = 1.6 \times 10^{-2}$ and 2.3×10^{-3}). There were no significant changes in the amplitudes of the other components.

Although the group-averaged waveform of the CAEP was distorted somewhat by toluene (Fig. 3), there were no statistically significant effects on latencies or amplitudes.

When the EEG was synchronized by clicks presented at 7.4/sec, spectral peaks were evident at 7.4, 14.8, and 22.2 Hz, but toluene had no significant effect on power of these spectral peaks.

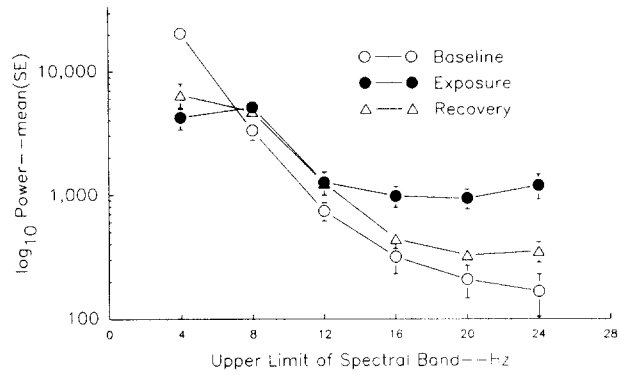

FIG. 2. Changes in visual cortex/reference integrated EEG spectral power bands before, during, and after exposure to 8000 ppm toluene.

Somatosensory-Evoked Potential

In Fig. 4 the amplitudes of SEP components are shown for the several recordings made during the test session. In contrast to our earlier results with Fischer-344 rats, 8000 ppm toluene did not

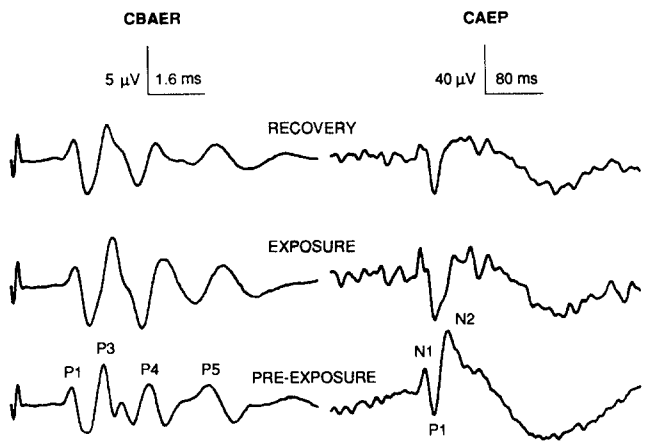

FIG. 3. Group-averaged waveforms for brainstem and cortical auditory-evoked potentials elicited by clicks before, during, and after exposure to 8000 ppm toluene.

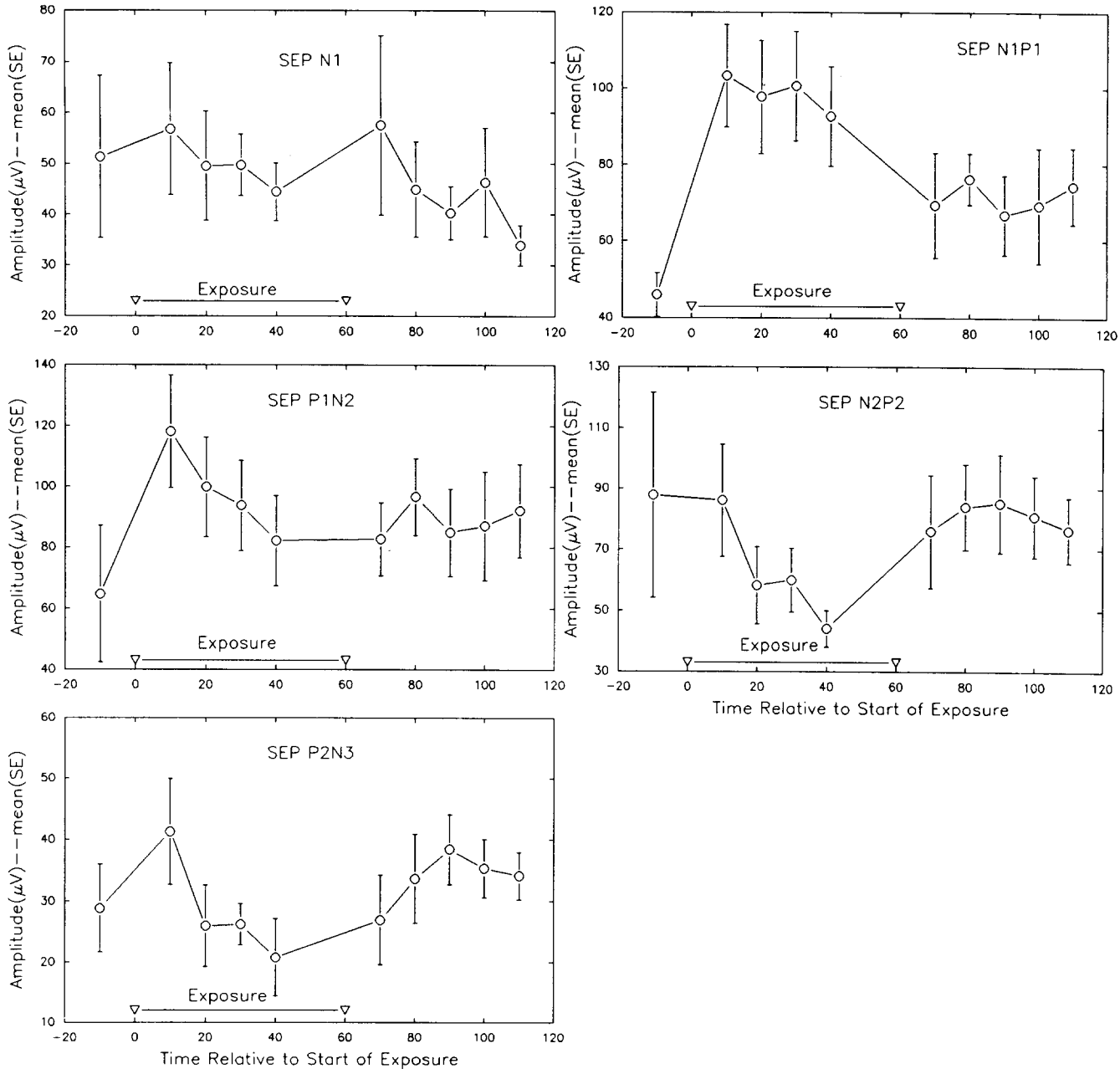

FIG. 4. Changes in peak-to-peak amplitudes of SEP components at various times in relation to exposure to 8000 ppm toluene. At 50 min after the start of exposure TSTBAT was run instead of the SEP.

increase the amplitude of the N1 component. When examined at the 30-min test (a time comparable to our previous study), the N1P1, but not P1N2, component was significantly enlarged, $t(6)=5.2$, $p=2.0\times10^{-3}$. The P1N2 component was transiently enlarged at an earlier time [at 10 min $t(6)=3.27$, $p=1.7\times10^{-2}$]. After that, P1N2 amplitude declined. Both the N2P2 and P2N3 components tended to become smaller than normal after 10 min of exposure (Fig. 4).

Because the lack of effect on N1 and the occurrence of only a transient enlargement of P1N2 probably reflected the development of suppressant effects of toluene as the exposure progressed, the rats were exposed for 20 min to 3000 ppm toluene and the SEP was repeatedly obtained. As shown in Fig. 5, all component means increased over time; at the 20-min test, the changes were significant for the three middle components [p(N1P1)$=5.3\times10^{-3}$, p(P1N2)$=3.2\times10^{-3}$, p(N2P2)$=3.7\times10^{-4}$].

Visual-Evoked Potentials

Although the group mean waveform was distorted (Fig. 6), PREPs were not significantly altered by toluene when measured after 50 min of exposure. However, toluene disrupted the rhythmic

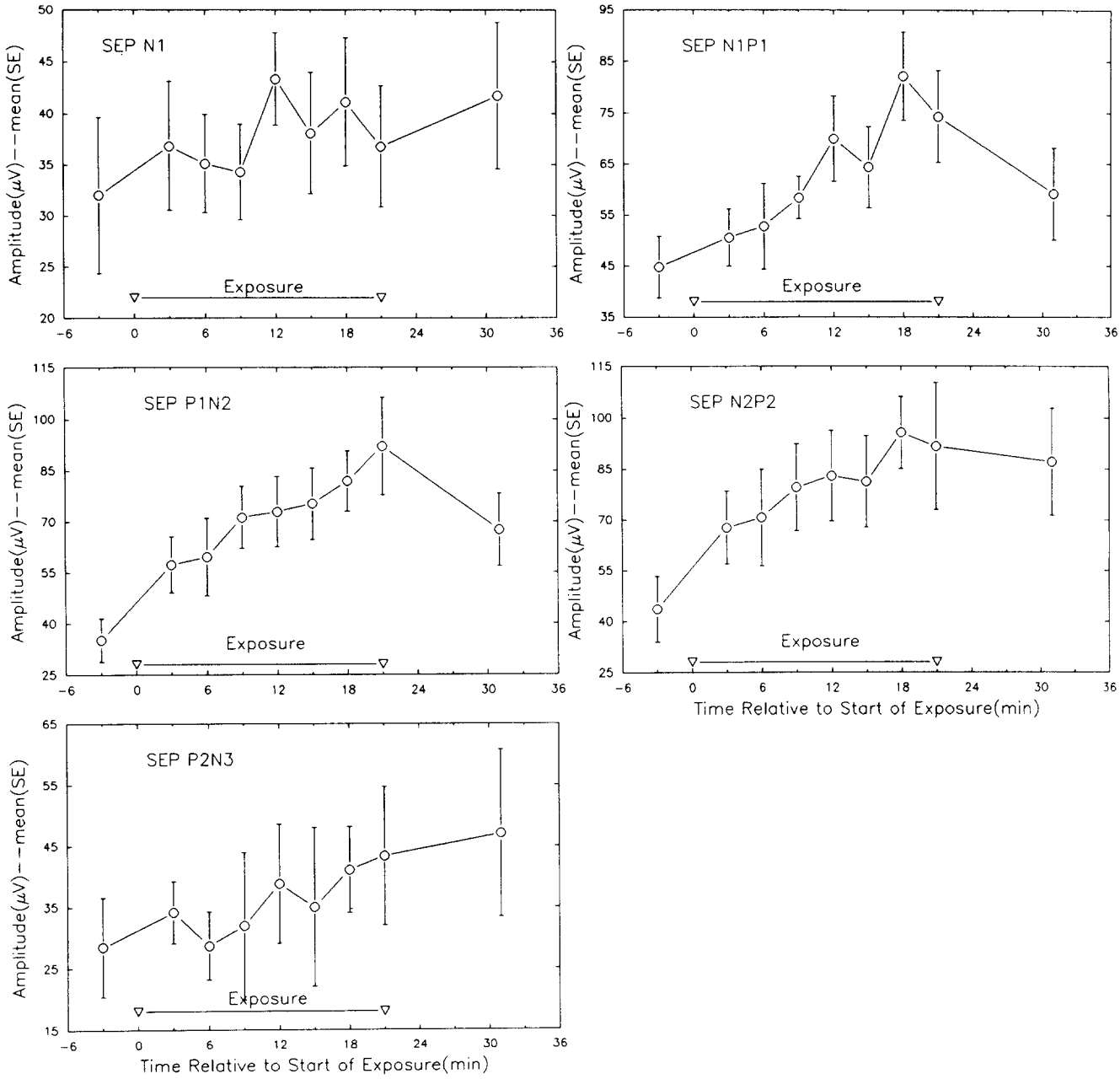

FIG. 5. Changes in peak-to-peak ampltiudes of SEP components at various times in relation to exposure to 3000 ppm toluene.

driving in the SSPREP (Fig. 6), and this was reflected by a significant decrease of 52% in the whole-wave integrated score ($p = 3.7 \times 10^{-2}$).

Analyses of FEPs revealed significant changes in the amplitude, but not latencies, of several waveform components (Fig. 7). P1N1 amplitude tended to increase in size (by 39%; $p = 7.7 \times 10^{-2}$), whereas later components significantly decreased by 45 to 57% [$p(\text{P3N3}) = 9.8 \times 10^{-3}$, $p(\text{N3P4}) = 1.1 \times 10^{-2}$].

No changes in the EEG associated with 7.4/sec repetitive flashes were observed.

To examine FEP oscillations (Fig. 8), the averaged 2-sec epochs recorded with a 15- to 55-Hz bandpass were full-wave rectified and low-pass filtered (2 Hz). They were then integrated in 400-msec bands as well as across the whole epoch (to obtain a single score). Spectral analysis was also carried out. Three spectral peaks were evident, averaging in frequency, before exposure, 18.5, 27.1, and 34.0 Hz. As shown in Fig. 9, integrated amplitude was largest early in the sampling epoch, then declined. Whole-wave integrated FEP oscillatory amplitude (Fig. 10) increased during the first 20 min of exposure [$p(10\text{ min}) = 1.1 \times 10^{-2}$], leveled off, and then decreased; it increased again early in the recovery phase [$p(70\text{ min}) = 4.1 \times 10^{-4}$], declining thereafter. Spectral power of the 34-Hz peak, but not the others, exhibited a similar relationship to exposure conditions (Fig. 10). Spectral

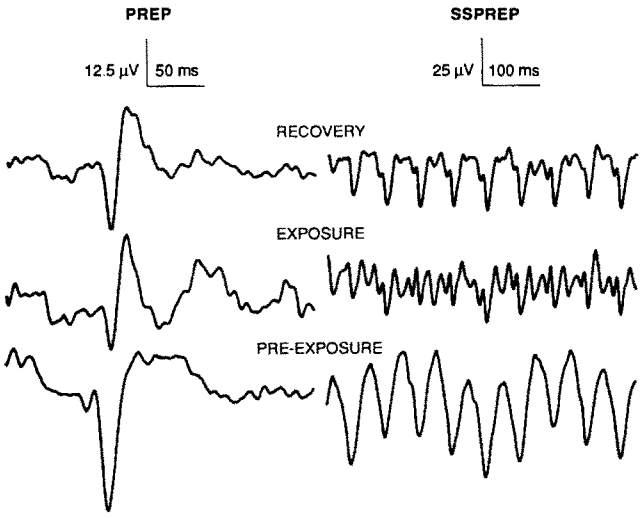

FIG. 6. Group-averaged waveforms for EPs elicited by checkerboard reversals before, during, and after exposure to 8000 ppm toluene.

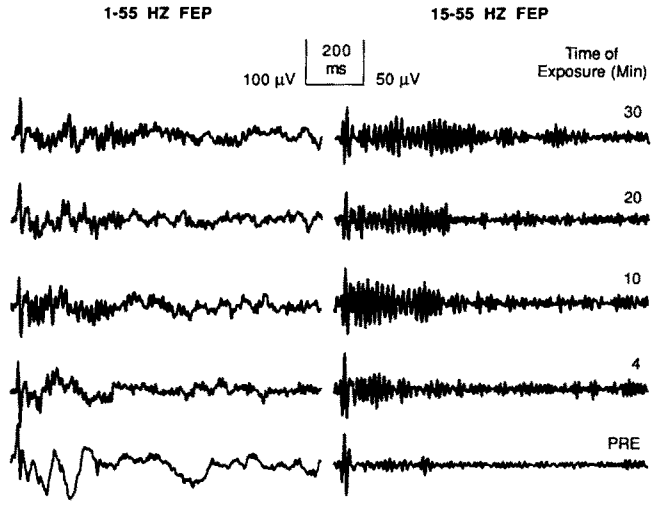

FIG. 8. Example from one rat of averaged FEPs obtained with a long (2 sec) recording epoch before and at various times during exposure to 8000 ppm toluene. Visual cortex oscillations were more evident with the restricted recording bandpass and increased gain.

power was significantly larger at 20 and 70 min (10-min recovery) than during baseline [$p(20) = 2.1 \times 10^{-2}$, $p(70) = 9.0 \times 10^{-3}$]. We also examined the frequency of the largest peak in the FEP spectra. During baseline this averaged 25.5 Hz. It increased to a maximum of 33.7 Hz at the 20-min test ($p = 1.96 \times 10^{-2}$). It declined thereafter to a value of 26 Hz 50 min after the end of exposure.

As indicated above, the amplitude of oscillations in averaged waveforms time-locked to the flash were largest early in the epoch. As noted before, this could be due to either a true decline in amplitude in the epoch, or a greater temporal variability later in the epoch, resulting in only an apparent decline due to averaging of sample epochs. Because preliminary data suggested that the oscillations were not elicited by the flashes, 32 to 48 single sample epochs were obtained with and without the photostimulator on. They were individually rectified and smoothed before averaging, thus eliminating amplitude changes due to temporal "jitter." This procedure showed that oscillatory amplitude remained constant throughout the recording epochs; also, it increased during exposure with or without the presence of flashes [$p(\text{flashes}) = 4.5 \times 10^{-3}$; $p(\text{without flash}) = 2.6 \times 10^{-3}$] (Fig. 11).

DISCUSSION

This study confirmed, in Long-Evans rats, a number of observations made by Rebert *et al.* (15) concerning the effects of inhaled toluene on sensory-evoked potentials in Fischer-344 rats. As in Fischer-344 rats, toluene increased, in some cases transiently, the amplitude of certain components of the SEP, FEP, and BAER. Toluene increased BAER component latencies and interwave times, decreased late components of the FEP, induced high-frequency oscillations in the visual cortex, and produced both facilitatory and suppressant effects on SEPs.

Changes in latencies of BAER components were considerably beyond the approximately 70 μsec expected in relation to the 1°C decrease in body temperature—latencies increased by 116 (P1) to

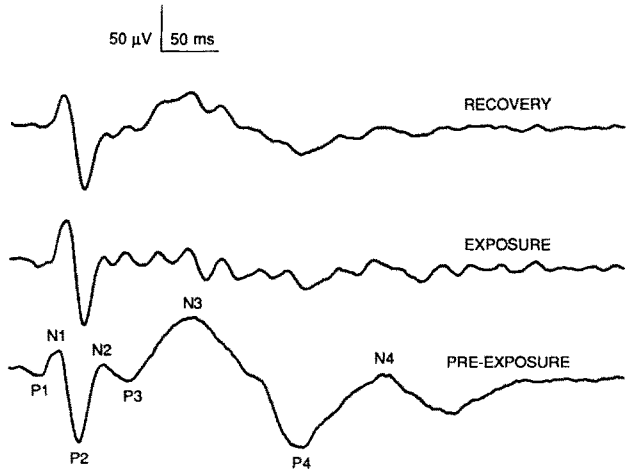

FIG. 7. Group-averaged FEPs before, during, and after exposure to 8000 ppm toluene.

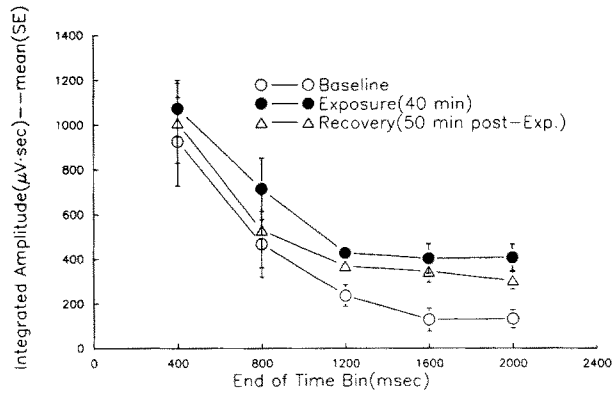

FIG. 9. Integrated amplitude of visual cortex oscillations for 400 msec time bins before, during, and after exposure to 8000 ppm toluene.

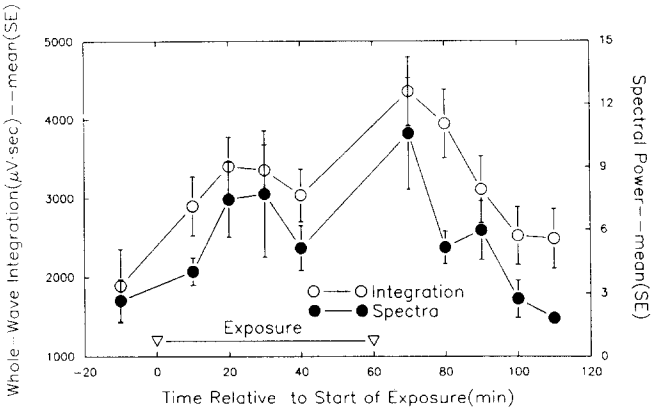

FIG. 10. Changes in whole-wave integration and spectral peak power of visual cortex oscillations at various times relative to exposure to 8000 ppm toluene.

475 (P6) μsec. This is consistent with previous observations when body temperature was better controlled in most conditions (15). The shape of the BAER differed somewhat from that typically observed in Fischer-344 rats. We have observed before (unpublished) that the P2 component is more pronounced, and the P6 component is less pronounced in Fischer-344 than Long-Evans rats. In our previous study we observed a tendency (unreported) for middle components of the BAER (e.g., N3P4) to be reduced in amplitude by toluene—this effect was significant in this study. As before, late components were enhanced. The decreased conduction time in the brainstem auditory pathways did not translate into a statistically reliable increase in components of the CAEP, although there was a tendency toward prolonged latency of late CAEP components.

Long-Evans rats appeared to be somewhat more sensitive than Fischer-344 rats to suppressant effects of toluene on the SEP. The N1 component was not much affected by exposure to 8000 ppm toluene in the Long-Evans rats. The N1P1 component increased in amplitude and remained enlarged for at least 40 min, but the P1N2 component was only transiently enlarged, and not significantly so at an exposure time comparable to the exposure time in the Fischer-344 rats. However, as in the Fischer-344 rats, the later components tended to be suppressed rather than enhanced by toluene. Although the pattern of effects among components was somewhat different at 8000 ppm than observed in Fischer-344 rats,

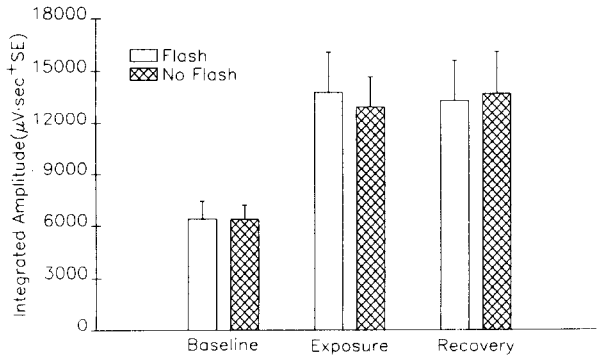

FIG. 11. Integrated amplitude of visual cortex oscillations in relation to toluene exposure, with and without the presence of flashes.

the results were generally similar to those obtained before, and are consistent with a greater sensitivity of Long-Evans rats to suppressant effects of toluene. This conclusion was supported by results of the exposure of Long-Evans rats to 3000 ppm toluene. This exposure resulted in an increasing enhancement of P1N2 amplitude as a function of exposure time and enhancement, rather than suppression, of the N2P2 component—this effect was just like that observed in Fischer-344 rats exposed to 8000 or 5000 ppm toluene. Also, there was less of an amplitude increase of the P2N3 component caused by 3000 ppm, i.e., as observed with Fischer-344 rats, later components appear to be more sensitive than earlier ones to toluene's suppressive effects.

Because in the second of our two previous experiments with Fischer-344 rats quantifiable FEPs were not obtained, conclusions about the effects of toluene on FEPs could be drawn with less than full confidence, even though the group-averaged waveforms of that experiment exhibited the expected changes. In this experiment with Long-Evans rats we obtained adequate FEPs, and toluene had essentially the same effects as previously observed in Fischer-344 rats. As in Fischer-344 rats, the late components (P3N3–P4N4) were substantially reduced, but the enhancement of early components was only marginally significant in Long-Evans rats [p(P1N1) = 0.06].

High-frequency oscillations observed in FEP epochs were more prominent in the Long-Evans rats than the Fischer-344 rats, and much more evident when the records were obtained with modified acquisition parameters (higher gain and more stringent filtering). However, we discovered here, somewhat circuitously, that the oscillations were not time-locked to, or a consequence of, the flashes, but reflected a change in spontaneous activity (not strikingly evident in the spontaneous EEG records). The previous suggestion that FEP spectral peaks increase in frequency with exposure to toluene was also confirmed in this study.

We extended our previous observations to parameters of the spontaneous EEG, other EPs (CAEP and PREP) and steady-state FEPs, CAEPs, and PREPs. Statistically, our results on the PREP were consistent with the report by Dyer *et al.* (5), indicating lack of effects of toluene on that response. However, our group-averaged waveforms suggested some distortion of PREPs by toluene, an effect that might be confirmed in an experiment with greater statistical power and, perhaps, with different exposure concentrations and/or examination earlier during exposure. The depression of SSPREP amplitude further suggests some effect on mechanisms that mediate the PREP. No effects on the CAEP or on spectral peaks of other SSEPs were detected.

Our EEG findings were consistent with observations in cats reported by Alcaráz *et al.* (1), who observed enhancement of theta activity, and Peréz *et al.* (10), who noted the induction of 20- to 30-Hz oscillations in visual cortex. Also, Takeuchi and Hisanaga (20) reported that 4-hr exposure of rats to 4000 ppm toluene increased the incidence of hippocampal theta activity. As far as we know, and as summarized by Benignus (2,3), human EEGs have not been recorded during exposure to more than 200 ppm toluene; at that level the EEG was unchanged (19).

We have shown that toluene affects the spontaneous EEG in several ways and alters electrophysiologic manifestations of activity in auditory, visual, and somatosensory pathways. Some of the changes during short-term acute exposures were consistent with phases of "excitation" and "suppression" of the nervous system reported for a variety of volatile anesthetics (21), but it remains to be determined if the profile of multisensory effects, and intramodality differences (e.g., early and late SEP components), are similar for various volatile substances. Other common components of solvent mixtures include methylene chloride, hexanes, heptanes, xylenes, and acetone. Because of their structural similarity to toluene, the xylenes might be expected to have similar effects.

The hexanes and heptanes, however, may not—at high concentrations they cause behavioral seizures that are antagonized by toluene (11).

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