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Effects of Toluene, Halothane and Ethanol Vapor on Fixed-Ratio Performance in Mice[1]

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MOSER, V. C. AND R. L. BALSTER. *Effects of toluene, halothane and ethanol vapor on fixed-ratio performance in mice.* PHARMACOL BIOCHEM BEHAV 22(5) 797–802, 1985.—The behavioral effects of inhalation of the vapors of volatile compounds representative of different chemical groups were studied in mice under conditions where behavior and exposure concentrations could be concurrently monitored. The magnitude and time course of the effects of toluene, halothane and ethanol inhalation on fixed-ratio (FR) responding were compared. The subjects were trained to lever-press under a FR-100 schedule of water reinforcement. Daily operant sessions took place in the exposure chambers, and solvent exposures were conducted once a week. The test exposures lasted for 20 min, and the sessions continued until the subjects resumed baseline rates of responding to give a measure of recovery. All solvents produced concentration-dependent response rate decreases, and only halothane showed any evidence of response rate increases at low concentrations. Halothane quickly produced maximal response rate-decreasing effects and recovery was rapid, while the effects of toluene became progressively greater during the exposure and recovery was prolonged. Ethanol displayed the most rapid onset and recovery of effects. Thus, these solvents produced somewhat similar effects on FR responding but displayed potency and time course differences.

Solvents Toluene Halothane Ethanol Inhalation Operant behavior Mice

THE inhalation of organic solvent vapors can produce profound behavioral effects in humans and animals. This route of administration has particular relevance to studies of general anesthetics, solvents for use in industry and the home, and solvents used recreationally. In spite of the widespread human exposure to solvent vapors, there are few systematic studies characterizing their behavioral effects. Studies of effects on laboratory animal behavior have been important for establishing the behavioral pharmacology of drugs and other chemicals administered by oral or parenteral routes. Therefore, we have undertaken to examine the effects of inhaled organic solvent vapors on the conditioned behavior of mice. We recently described an approach [1] for the concurrent measurement of solvent vapor concentrations and schedule-controlled responding of mice during and following exposure to 1,1,1-trichloroethane vapors. The apparatus described therein allows for rapid changes in chamber vapor concentrations during operant sessions and is particularly well-suited for examining the temporal relationships between vapor concentration and the behavioral effects of acute exposures. The compounds chosen for this study were toluene, a widely used industrial solvent; halothane, a popular volatile general anesthetic; and ethanol, a common central nervous system depressant. In addition to the large extent of exposure to these agents by the general population, the deliberate inhalation of each has been reported. Toluene appears to be preferred by solvent abusers [22] and halothane is self-administered primarily by health personnel [4,27]. Ethanol is nearly always abused by oral administration, but inhalation of the vapors to achieve euphoria has also been reported [7]. This paper reports a comparison of the acute effects of these three volatile compounds representing different chemical classes and human exposure situations using standard behavioral pharmacological methods.

METHOD

Animals

Adult CD-1 male mice were used. A separate solvent-naive group was tested with each compound. Eight subjects were used in the study of toluene, nine for halothane, and ten for ethanol. Mice were housed individually, with food available ad lib. Water access was gradually decreased over a two-week period to a final daily intake of 2.0 ml.

Apparatus

The behavioral sessions took place in an exposure system which has been described previously [1]. Briefly, the flow of

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air through the chamber was regulated via flowmeters to adjust the proportion which was bubbled through the solvent. The flask containing the solvent was maintained at a constant temperature (0°C for toluene and halothane, 34°C for ethanol). The vapor-laden air emerging from the flask was diluted with clean air and pumped into the exposure chamber at a constant rate (10 l/min) which allowed the chamber concentration to reach 99% of the plateau concentration within 2 min. A portion of the exiting air was continuously smapled by a single-wavelength monitoring infrared (IR) spectrometer (Miran 1A, Foxboro Analytical, North Haven, CT) to provide on-line analysis of the solvent vapor concentrations. The wavelength chosen to monitor each vapor was—toluene 13.75 μ, halothane 8.75 μ, and ethanol 9.20 μ. The IR spectrometer was calibrated using a closed-loop system for each solvent. The absorbance was linearly proportional to concentration over the range of concentrations used in this study. The exposure chambers were stainless steel cannisters with a lid which supported the response lever, water delivery trough, and stimulus light. Thus, the behavioral sessions were carried out while the subjects received exposure to either air or the solvent vapors. Schedule contingencies and behavioral data recording were carried out by a microprocessor (MCS, Micro Interfaces, Inc., Minneapolis, MN). Response and reinforcement data were collected for successive 5-min segments of the session. Cumulative response records and continuous IR absorbance records were also obtained.

Procedure

Sessions were conducted five days per week, Monday through Friday. The subjects were shaped to lever-press for water presentation (0.05 ml) and subsequently trained under a FR-100 schedule during 30-min sessions. Average response rates in each 5-min segment of the session were computed each day. When stable performances were obtained the solvent exposures were initiated. Solvent test days were once a week (Thursdays or Fridays), and data from one day each week (Tuesdays or Wednesdays) during vapor testing were averaged together for each subject to serve as that subject's control. The order of vapor concentrations tested for each subject was determined by a latin-squares design. These concentrations were: toluene—500, 1000, 2000, 3200, and 5000 ppm; halothane—1000, 2000, 3000, 4000, 5000, and 6000 ppm; and ethanol—14,600, 20,000, 27,400, 37,400 and 51,200 ppm. On test days, the session began with air exposure for 5 min to assure that each subject met a criterion of responding within 25% of average response rates during the comparable portion of the previous control sessions. If this criterion was not met, the subject was not tested and the session continued with air for the usual 30 min. When the criterion was met, the solvent vapor was turned on at 5 min, and off after 20 min of vapor exposure. The session continued until recovery occurred, defined by a criterion of responding within 25% of average rates of responding during the 25–30 min segment of control sessions, or until 35 min had elapsed. Thus, the maximal possible length of the behavioral sessions on test days was 60 min.

Data Analysis

Concentration-effect curves were constructed by averaging the data for all subjects for each solvent using the response rates corresponding to the last 15 min of solvent exposure (at which time solvent concentrations in the chamber were stable). Since the concentration-effect data was sigmoidal, only the linear portions of the curves were analyzed by least squares regression after $\log_{10}$ transformation of the concentrations. An EC50 (concentration predicted to decrease mean response rates by 50%) and 95% confidence limits were calculated from the regression line. Significant concentration effects for each solvent were determined by a one-way repeated-measures analysis of variance of the raw data followed by Dunnett's t-test. Level of significance was $p<0.05$. In addition, average rates of responding during each 5 min of the exposure were calculated as the percent of control rates during that segment for each mouse and averaged. Recovery time is reported as the median amount of time necessary for responding to reach control values at each concentration.

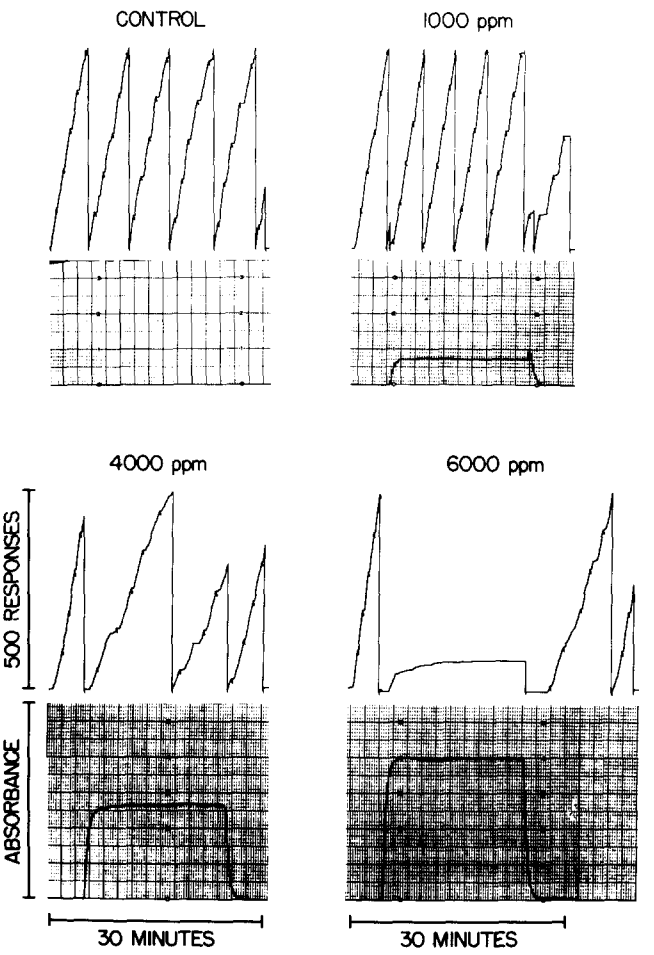

FIG. 1. Cumulative response records and vapors concentration plots as a function of time for several concentrations of halothane tested in one subject responding under a fixed ratio 100 schedule. The cumulative recorder pen steps up with each response and moves across the paper with time. Pen offsets indicate the delivery of the reinforcer. The pen was reset after every 500 responses as well as at 5 and 25 min, which indicates the time at which the solvent vapor was turned on and off. Absorbance of the solvent vapor was proportional to concentration.

Chemicals

The solvents used were toluene (T-324, Fisher Scientific

TABLE 1

RELATIVE POTENCIES OF TOLUENE, HALOTHANE AND ETHANOL FOR DECREASING RATES OF RESPONDING UNDER A FIXED-RATIO SCHEDULE OF WATER REINFORCEMENT IN MICE

	Toluene	Halothane	Ethanol
EC50 (ppm)*	1853	3656	26,879
(95% confidence limits)	(1374–2183)	(3119–4571)	(23,434–30,399)
slope†	−163.3	−252.0	−147.7
(S.E.)	(26.6)	(57.3)	(17.3)

*Concentration expected to decrease rates of responding to 50% of control levels as determined by least squares linear regression.

†Slope of the linear portion of the concentration effect curve after $\log_{10}$ transformation of concentration in ppm.

Co.), halothane (Fluothane^R, Ayerst Laboratories, Inc.), and 95% ethanol (USP). All concentrations are expressed in ppm. The ethanol vapor concentrations in ppm represent pure (100%) ethanol.

RESULTS

All mice maintained steady baseline rates of responding throughout all studies. However, due to the wide range of control response rates between subjects (0.4 to 2.1 responses/sec), solvent effects were calculated as a percent of each subject's control value in the graphical presentation of the data. Responding always returned to baseline rates during the sessions the day after solvent test sessions.

Figure 1 shows the cumulative response and IR absorbance records for one representative subject during exposure to various concentrations of halothane. Typical control response patterns of a high steady rate of responding leading to water delivery with a short post-reinforcement pause are evident in the first 5 min of each cumulative record. The rapid time course for changes in solvent concentration within the chamber is evident in the IR absorbance records. The magnitude and time course for response rate disruption can be seen to correlate with solvent levels by comparing absorbance and cumulative response records. At 1000 ppm of halothane, response rate throughout the exposure was somewhat increased. This was not seen during toluene or ethanol exposures. At 4000 ppm of halothane, response rate decreases and disruption of patterning were evident within 5 min of the onset of the vapor concentration, and did not progress further during the exposure. Baseline response rates resumed immediately following the termination of exposure. Halothane at 6000 ppm rapidly produced complete response suppression and 15 min were required for the subject to resume a control rate of responding.

Concentration-effect curves for all three solvents are presented in Fig. 2. All solvents produced a concentration-dependent decrease in response rates with nearly complete suppression at the highest concentrations tested. Halothane produced increases in rates of responding at low concentrations in 5 of the 9 subjects, but only rate-decreasing effects were statistically significant. In contrast, only one toluene-exposed subject and no ethanol-exposed subject showed evidence of a biphasic response rate function. The lowest statistically effective response rate-decreasing concentration

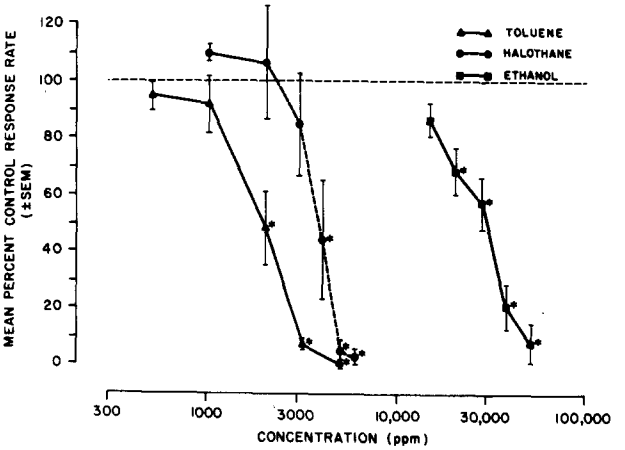

FIG. 2. Concentration-effect curves for the effects of toluene, halothane and ethanol on overall rates of responding under a fixed ratio 100 schedule during the last 15 min of 20-min exposures. Values are the mean percent of control rates of responding±S.E.M. *Significantly different from control ($p<0.05$).

of toluene was 2000 ppm, for halothane 4000 ppm, and for ethanol 20,000 ppm. Linear regression analyses of these lines produced the point estimates and slopes listed in Table 1. Significantly different EC50 values were obtained for each solvent since the 95% confidence limits for each solvent did not contain the EC50's of the others. Toluene was most potent, with halothane about one-half as potent and ethanol 14 times less potent than toluene. The concentration-effect curve for halothane was somewhat steeper than the curve for the other compounds.

The time course for solvent effects over the last 15 min of the 20-min exposures is shown in Fig. 3. The average rates of responding as a function of concentration are shown for successive 5-min segments of the exposure. In general, each of the three vapors exhibited effects by the second 5 min of exposure without a pronounced progressive disruption with continued exposure. This was particularly true for ethanol (right panel) where only at 37,400 ppm was there any clear trend towards progressive effects. The progressive effect of this concentration occurred in only 5 of the 10 subjects, and

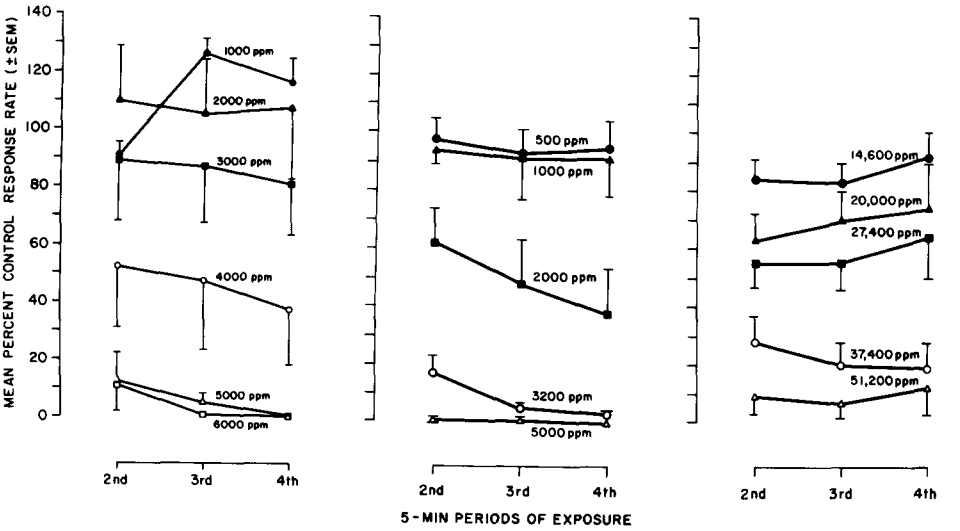

FIG. 3. Time course for behavioral effects during exposure to halothane (left panel), toluene (middle panel), or ethanol (right panel) as a function of concentration in mice responding under a fixed ratio 100 schedule. Values are the mean rates of responding expressed as percent of control rates during each of the last three 5-min periods of the 20-min exposure session. The first 5-min period was omitted since chamber concentration was changing during that period.

indeed some subjects evidenced within-session partial recovery of response rates at this and other concentrations of ethanol. This lack of progressive within-session effects of ethanol can be contrasted with the results for toluene (center panel). At 5000 ppm all subjects were maximally effected by the second 5 min of exposure. However, at 2000 and 3200 ppm, all but one subject showed either a progressive decrease in response rates or was maximally affected by the second 5 min of exposure. For halothane (left panel), the results were less consistent. At the highest concentrations (5000 and 6000 ppm), all but two subjects were maximally affected by the second 5-min period. These two subjects showed progressive effects. At 4000 ppm, six subjects evidenced progressive effects while three recovered somewhat during the exposure, and at 3000 ppm five were progressively affected and four showed recovery. At 1000 ppm, nearly all the subjects recovered partially from the second to the third 5 min of exposure. Thus, it would appear that toluene has some progressive effects as a function of exposure duration, whereas halothane and ethanol do not consistently produce progressive effects.

Figure 4 shows the recovery from the effects of each of the solvents after the chamber was purged. Subjects recovered most rapidly from the effects of ethanol where even at the highest concentrations control rates of responding were achieved within 15 min. For toluene and halothane there was a concentration-dependent recovery with 20–25 min required for recovery from the highest concentrations. Recovery from 3000 ppm toluene and 5000 ppm halothane was more prolonged than from an equipotent concentration of 51,200 ppm ethanol. There was some evidence that recovery from halothane was more rapid than from equipotent concentrations of toluene. For example, at 3200 ppm toluene, which decreased overall rates of responding to about (10% of control levels, Fig. 2), recovery required a median of 20 minutes. Recovery from an equipotent concentration of halothane (5000 ppm) occurred in a median of 15 min.

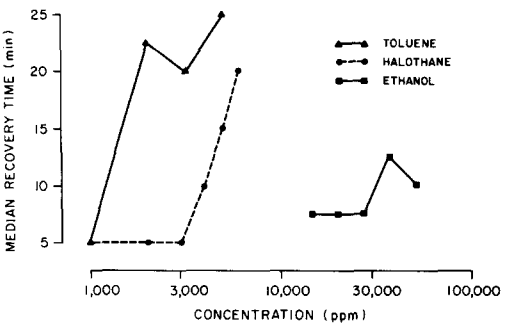

FIG. 4. Recovery from the behavioral effects of 20-min exposures to toluene, halothane or ethanol in mice responding under a fixed ratio 100 schedule. Values are the median latency for rates of responding to return within 25% of control rates as a function of concentration.

Halothane-exposed subjects rarely failed to resume control rates of responding within the 35 min recovery time, whereas many toluene-exposed subjects had not resumed responding when the session was terminated after 35 min.

DISCUSSION

The dynamic exposure system utilized allowed an examination of the magnitude and temporal patterns of inhaled solvent effects on schedule-controlled behavior in mice. The orderly results of this study showed that the inhalation of organic solvents can produce concentration-dependent behavioral effects similar to those seen with the administration of many other psychoactive agents. These results are in general very similar to those obtained earlier with another industrial solvent, 1,1,1-trichloroethane, using an identical protocol [1].

The monotonic effects on response rate produced by toluene and ethanol were somewhat in contrast to the biphasic effect produced by halothane. However, the response rate-

increasing effect produced by halothane was clearly evident in only half of the subjects. Only a few studies have examined the effects of halothane on schedule-controlled responding. Response rate increases were detected at similar concentrations in mice responding under a fixed-interval (FI) schedule following exposure (manuscript in preparation), but only decreases in response rates were reported in pigeons responding under a variable interval or a multiple FI FR schedule [9]. The range of rate-suppressive concentrations in this study (3000–6000 ppm) was comparable to effective concentrations in previous studies, as well as being applicable to human exposure. The median anesthetic concentration in man is 6000 ppm [21], which was the highest concentration tested here and which produced complete suppression of responding.

The effective concentrations of toluene reported here (2000–5000 ppm with 20-min exposure) are similar to those in the literature, which are in the range of 150–6400 ppm with exposure durations of 30 min to 4 hr. This is the first report of toluene effects on responding under a simple FR schedule. The monotonic concentration-effect curve is consistent with the effects of toluene in rats responding during the FR component of a multiple FR-differential-reinforcement-of-low-rates (DRL) schedule during exposure [6], or under a fixed consecutive number (FCN) schedule following exposure [29]. However, a biphasic effect on response rate as a function of exposure duration was evident in rats responding under a multiple FR FI schedule after exposure [11]. Stimulation of responding has also been reported in mice and rats responding under a FI or DRL schedule [6, 12, 13, 23] and in pigeons under a FCN schedule [28].

Ethanol has most commonly been studied by injection or oral routes of administration, and only infrequently by the inhalation route [14,15]. Ethanol vapors produce only response rate decreases in mice responding under a FI schedule after exposure (manuscript in preparation). Higher concentrations were necessary to produce those effects than were used in the present study, possibly due to the rapid recovery of effects following exposure, as was observed in both studies. Following systemic ethanol, only response rate suppression was also observed in pigeons under a FI schedule, alone or as a component of a multiple schedule [18,20], and in rats under a DRL schedule [19]. However, ethanol often produces a biphasic dose-effect curve using FR schedules. This was reported in rats responding under a FR or DRL schedule [16], and in pigeons under a FR schedule alone [18], or as a component of a multiple FR FI [20].

Overall generalizations summarizing the behavioral effects of volatile solvents are difficult since experiments have been conducted during or after exposures of varying durations, concentrations, and exposure regimens. It is evident that all of these factors are important in determining the effects of solvents, and furthermore the degree of importance of each factor varies according to the solvent. Perhaps a more useful approach to examine this issue would be to test many solvents under the same experimental protocol, as we have begun to do here.

An examination of the time course of solvent effects can suggest relationships between behavioral effects and exposure duration. With halothane and ethanol, little change in response rate decreases was seen over time. However, in pigeons, responding progressively decreased over a 16-min exposure at concentrations of halothane of 4000 ppm and higher [9]. The progressive effects of toluene obtained here are in agreement with those of Glowa [13]. He reported that, in mice responding during 4-hr exposures to toluene, the progression of effects at 2000 ppm possibly indicated increasing blood and brain levels for up to 2 hr. Similarly, in rats the effects of a low concentration of toluene on responding changed as a consequence of increasing exposure duration [11]. With halothane and toluene, there may be species differences in the rate of vapor uptake. Studies to further pursue this subject would include longer exposure durations and measurements of blood and/or brain solvent levels.

The elimination of solvent vapor may be indicated by the recovery of behavioral effects. The half-life for elimination of halothane vapor in mouse brain has been reported to be less than 10 min [5], whereas that of toluene is approximately 60 min in both mice and rats [2,3]. Therefore, if behavioral effects are related to blood levels of these compounds, recovery from halothane would be expected to be more rapid than recovery from toluene. There was some evidence that this was the case in our study. On the other hand, the slow zero-order rate of ethanol metabolism in mice has been described [8,15]. However, recovery from ethanol in this study was equal to or more rapid than that of halothane. It has been reported that ethanol administered via inhalation is eliminated faster than by other routes of administration [8]. This rapid recovery from inhaled ethanol has been replicated in other operant experiments in our laboratory, but not using measures of muscular coordination [24]. The possibility exists that a rapidly developing "acute" tolerance [10,26] is responsible for the very rapid recovery observed at all concentrations. Correlations of behavioral effects with blood and brain ethanol levels during and after inhalation exposure would help clarify this discrepancy.

A possible mechanism for the behavioral disruption we observed during solvent exposure is the odor and irritant properties of these compounds. These properties could account for concentration-dependent effects. If this were true, however, recovery latencies would not be expected to greatly exceed the time it takes to clear the chamber of solvent vapor. The longer, concentration-dependent recovery latencies observed with halothane and toluene are more consistent with a central effect. Gross observation revealed that mice exposed to only the highest concentrations of these solvents showed any observable signs of mild eye and nose irritation. As further evidence, Nielsen and Alarie [25] reported that in mice inhaling toluene, respiratory rate was persistantly affected only at 6400 ppm and higher. On the other hand, the rapid recovery from the effects of ethanol do suggest that irritant properties may play a role in the behaviorally-disruptive effects of this solvent, and may explain why onset and recovery was more rapid than would be predicted by the pharmacokinetics of ethanol. Indeed, Kane *et al.* [17] reported that the respiratory rate of the mouse is decreased by 50% at approximately 27,314 ppm. This value is almost identical to the EC50 for response rate suppression obtained herein (26,879 ppm). A possible method by which to investigate central vs. peripheral effects would be to compare experiments using longer exposure durations and lower, less irritating concentrations of ethanol.

This study described the effects of concurrent solvent vapor exposure on operant behavior in mice. Analysis of responding during exposure provided a behavioral assessment of the time course and magnitude of these effects. The rapid removal of solvent vapors from the chamber allowed a measure of recovery. In addition, the use of an operant schedule which produces steady rates of responding facilitated the immediate detection of behavioral changes.

The slopes of all curves were extremely steep. Halothane displayed the steepest curve; only a 1.7-fold increase in concentration changed a behaviorally-inactive concentration to one which produced nearly complete response rate suppression (from 3000 to 5000 ppm). This illustrates the necessity of accurate verification of solvent vapor concentrations. Using this paradigm, it was found that toluene, halothane, and ethanol had generally similar effects on FR responding in mice. Differences in the patterns of behaviorally disruptive effects over time and recovery rates were observed. The behaviorally disruptive effects of ethanol may be due in part to peripheral and respiratory irritation. Studies of this type further describe the behavioral pharmacology of inhaled volatile compounds.

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