TOLUENE:

DEVELOPMENT OF A BIOLOGIC STANDARD

FOR THE INDUSTRIAL WORKER

BY BREATH ANALYSIS

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16. Abstracts A comprehensive study to determine the biologic threshold-limit-value of toluene (108883) utilizing the breath-analysis decay curve (BADC) was conducted. Twenty healthy adults were exposed to vapor concentrations in an environmentally controlled chamber. The exposure consisted of both steady nonfluctuating concentrations as well as widely fluctuating concentrations. Eleven male subjects were exposed to 0, 20, 50, and 100ppm toluene for 1, 3 or 7.5 hr. Female subjects were exposed to 100ppm for 1, 3 or 7.5 hr. Breath and urine samples were taken. Neurological studies, cardiopulmonary-function tests, and cognitive testing were performed. Subjects exposed to toluene at 100ppm for 7.5 hr/day, 5 day/wk demonstrated deleterious effects on visual-evoked-response, increased errors in an alertness test and irritation of the nasal-mucosa. Subjects at 100ppm 3 hr/day, 5 day/wk noted an increase in eye, nose, and throat irritation. Blood-levels were relatively constant at exposures of 50 and 100ppm. Hippuric acid (495692) excretion increased in a dose-dependent manner. The biologic threshold-limit-value for toluene workers is suggested to be the upper-limit of the range of BADC of those exposed 7.5 hr/day for 5 days.

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INDUSTRIAL WORKER BY BREATH ANALYSIS

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TOLUENE

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A comprehensive study has been carried out with volunteer subjects on the effects of repeated controlled exposures to the vapors of toluene (toluol). The study was carried out with healthy subjects, both male and female. During the study, particular emphasis was placed on two areas: (1) the subject's health, including measurements of pulmonary, cardiovascular, and central nervous system functions, and (2) the relationship of the magnitude of exposure to toluene body burden as demonstrated by the measurement of toluene or its metabolite in blood, urine, and breath. This study presents a baseline for additional studies needed to assure a healthy and safe environment wherever this chemical is present in the workplace.

This report includes the observations made and the summary of the data collected during the study. The results are reviewed in the light of other recent studies[1,2] and excerpts from the criteria document prepared by NIOSH[3]. A recommendation for a "biologic threshold limit value", utilizing the breath analysis decay curve (BADC), is presented, along with a preliminary estimate of the magnitude of the safety factor found in the 1971 TLV of 100 ppm.

EXPERIMENTAL

Healthy adults of both sexes were exposed to closely regulated concentrations of toluene vapor in a controlled-environment chamber. The study was designed to simulate the type of exposure encountered by sedentary workers in an industrial setting, and consisted of both steady, non-fluctuating concentrations as well as widely fluctuating concentrations of toluene.

Exposure Schedule:

The vapor exposure sequence is presented in Table I. The sequence was initiated with male subjects who were exposed to toluene vapor concentrations of 0, 20, 50, and 100 ppm for periods of 1, 3, or 7-1/2 hr. The female subjects were exposed to 100 ppm also for periods of 1, 3, and 7-1/2 hr. The vapor concentrations in the controlled-environment chamber were not permitted to fluctuate widely except for the male exposures during week 5 when the wide fluctuation study was performed. Figure 1 illustrates the planned daily fluctuations in vapor concentration during days 1 and 2 of week 5.

One-hr (Group III) and 7-1/2-hr (Group I) subjects entered the environmental chamber at 9:00 A.M. each day while the 3-hr (GroupII) subjects entered at 10:00 A.M., at which time the 1-hr subjects exited. The 3-hr subjects exited at 1:00 P.M., while the 7-1/2-hr group exited at 4:30 P.M. The latter group was served lunch in the chamber. There were never more than 8 subjects in the chamber at one time.

The subjects were generally sedentary during their exposure in the environmental chamber. All male subjects were given brief periods of controlled exercise. The 1-hr and 3-hr subjects exercised on bicycle ergometers at a level of approximately 350 KPM for 6 min midway through each daily exposure. The 7-1/2-hr male subjects were exercised an additional 5 min at approximately 750 KPM.

This exercise period was combined with the cardio-pulmonary function studies on day 4 of each week. The exercise period was deleted for the 7-1/2-hr subjects during week 5 of the study.

Subjects:

The subjects were selected from the Caucasian, middle class, working population of the Milwaukee metropolitan area. They were recruited for this study by a private employment agency. Each subject who completed a section of the study received $2.50 per hr spent at the laboratory, plus overtime, with a 3-hr minimum payment for the Saturday morning medical surveillance check. After the objectives of the study and the nature of the procedures to be used were fully explained to them, all subjects signed an informed consent form, a copy of which is attached as Appendix I. One male faculty member volunteered as a 1-hr subject during week 5.

Eleven healthy males volunteered. Their ages ranged from 20 to 47 years, height from 170 to 187 cm, and weight from 66 to 89 kg. None was obese.

The ages of the 9 participating females ranged from 19 to 43 years, their height from 152 to 174 cm, and their weight from 50.5 to 88 kg. One was obese.

All subjects were cautioned to abstain from the use of drugs and to limit their use of alcohol to very moderate amounts. Subjects who were smokers were not allowed to smoke during their stay in the controlled-environment chamber. Subjects who underwent behavioral testing (3-hr and 7-1/2-hr) were asked to refrain from consuming any caffeine prior to the end of each day's study (1 hr post-exposure).

Most of the subjects had no other wage-earning job during the time of the study, and none experienced any known exposure to toluene outside of the laboratory.

Exposure Chamber:

All exposures to the vapor of toluene were conducted in a controlled-environment chamber 20' x 20' x 8' in size, which contained a 5' x 4' x 8' toilet facility and a 5' x 4' x 6-1/2' commercial audiometric booth. Both the toilet facility and the audiometric booth were ventilated with air from the chamber. Air flow through the chamber was approximately 1500 cu ft/min, and approximately 25% of this flow was exhausted. A slight negative pressure was maintained in the chamber at all times. Air temperature was 72 - 74° F, while relative humidity ranged between 45 - 55%. The toluene was introduced by sweeping the concentrated vapor from a warm flask with a stream of air into the chamber's circulating air. A reciprocal dual-piston pump maintained a steady flow of liquid toluene into the flask.

Chamber Concentration Control:

Each gallon of toluene (Fisher Scientific Co., Certified ACS) used to contaminate the chamber atmosphere was individually analyzed by gas chromatography and infrared spectroscopy (Beckman IR-10) before use. No impurities at levels greater than a few ppm were found.

Standards were prepared by filling Saran bags with room air pumped in sequence through a charcoal column, a wet test meter, a Drierite column, and a type N all-service gas mask cannister. After filling a bag with a known amount of clean, dry air, a known calculated amount of toluene was injected into the bag using a microliter syringe. Necessary amounts of toluene were calculated taking into account bag volume, air temperature, and barometric pressure. Calibration of analytical devices was accomplished by attaching a Saran bag standard to the necessary probe within the chamber. At least 3

standards were analyzed prior to allowing subjects to enter the chamber each day and then standards were analyzed periodically during the day.

Two completely independent systems were used to monitor the chamber atmosphere. In both cases, air was withdrawn from the chamber through a 1/4 inch I.D. polyethylene tube, through or past the analytical device, to a small diaphragm pump which discharged either back into the chamber or into an exhaust hood. Air flow rate through the sampling lines was about 7ℓ per min.

Contrary to our usual practice, gas chromatography (GC), rather than infrared spectroscopy (IR) was used as the primary monitoring and chamber concentration control device for toluene. Air from the chamber flowing through a small sample loop was automatically injected into the GC every 70 sec. The Varian Aerograph Model 1200 GC was equipped with a stainless steel column, 14" x 1/8", packed with Fluoropak 45/60 mesh. The column was preconditioned at 200° C for 24 hr prior to its use and throughout the study it was held at 200° C when not in use. Operating conditions were: carrier gas flow rate of 30 ml per min; column temperature,140° C; injection port,150° C; detector,250° C; air and hydrogen pressures,18 psig.

Infrared spectroscopy was used as the "backup" method because toluene does not have a unique absorption band in the infrared spectrum available to a Wilks MIRAN-I spectrometer. For the analysis, the 20-m cell was operated at a 5.25-m path length and the absorption band at 13.7 μ with a 2-mm slit was used. Despite interferences from ambient air and, apparently, from the subjects themselves, accuracy under these conditions was adequate to assure that the GC values were correct.

After each exposure ended, a calibration curve for the GC values was established with the computer using regression analysis on the standards that had been analyzed during the day. With that equation, peak height values read manually

from a strip chart were transformed into concentrations which were then used to calculate the required time-weighted averages and standard deviations for exposure increments.

Medical Surveillance:

Each subject was given a comprehensive medical examination prior to and after the last exposure day of the study. These examinations included a complete history and physical examination with the following laboratory studies: complete blood count, complete panel of clinical chemistries, a 12-lead electrocardiogram (EKG), and a pregnancy test (PREGNOSIS) for females. A complete blood count and the panel of clinical chemistries was repeated once per week on day 5 during the weekly exposures. Prior to each day's exposure, the subjects were given a brief medical examination which included blood pressure, temperature, subjective signs or symptoms, and urinalysis (Combistix®). During the time that they were in the environmental chamber, each subject's EKG (lead II) was continuously monitored by telemetry and recorded at hourly intervals. The subjects were under continual surveillance by medical personnel while they were in the study.

Breath Sample Collection and Analysis for Toluene:

Alveolar breath samples were obtained daily from each subject prior to entry into the environmental chamber, immediately upon exiting the chamber, and at the following times after exiting the chamber (post-exposure): 5, 15, 30 min; 1, 2, 3 hr. A 16-, 21-, and 23-hr post-exposure sample (usually identical to the pre-exposure sample) for Group I, II, and III, respectively, was also collected. Breath samples were all collected in 5-ℓ Saran bags. Sampling of

the Saran bag was accomplished by puncturing with a syringe needle.

A Varian Aerograph Model 2700 gas chromatograph equipped with a hydrogen flame ionization detector was used to determine toluene in the breath samples. The gas chromatograph (GC) was fitted with a stainless steel column, 5' x 1/8", packed with Apiezon L on Chromosorb W, 45/60 mesh. The column was preconditioned at 200° C overnight prior to its use. The operating conditions of the GC were as follows: carrier gas (nitrogen) flow rate of 40 ml/min; column temperature of 105° C; injection port, 210° C; and detector, 220° C. Both hydrogen and air were kept at 10 psig. Standards at 3 concentrations to bracket the unknown levels were prepared with purified air as diluent. A single injection was made because of the reproducibility of the analysis. The concentration of toluene in unknowns was obtained by direct comparison of peak heights to the standards. The minimal amount of toluene detectable in breath by this method was 0.001 ppm with an accuracy of ±0.05 ppm.

Fifteen min after the end of the exposure on the fourth day of week 2, females, a second alveolar breath sample was collected from each subject. This breath sample was slow-scanned in a Beckman® IR-10 infrared spectophotometer with a 10-m gas cell.

Blood Sample Collection and Analysis for Toluene:

At least 2 ml of blood was withdrawn from an antecubital vein of each subject prior to chamber entry on days 1, 3 and 5 of each week and the sample was analyzed for baseline toluene concentration. Additional blood samples for toluene assay were obtained immediately pre-exit from the chamber and 15 min post-exposure on these same days.

A 2-ml aliquot of blood was introduced into a 40-ml capped (Saran-lined) glass vial containing 1 ml aqueous solution of 1 ppm ethyl benzene as internal standard. The mixture was shaken and warmed at 37° C in a water bath. The headspace technique was employed for the analysis of toluene. One ml of the vapor was withdrawn and injected into a gas chromatograph. Samples were usually analyzed the same day they were obtained.

A Varian Aerograph Model 2700 Moduline® gas chromatograph equipped with a hydrogen flame ionization detector was used to determine the toluene levels in blood. The gas chromatograph was fitted with a stainless steel column, 3-1/2'x 1/8", packed with 25% Apiezon L on Chromosorb W, 45/60 mesh. The column was preconditioned at 200° C overnight prior to its use. Throughout the analysis for toluene in blood, the column was held at 200° C when it was not in use. The operating conditions of the GC were: carrier gas (nitrogen) flow rate of 30 ml/min; column temperature,150° C; injection port,220° C; and detector,200° C. A calibration curve (peak height ratio of toluene to ethyl benzene versus concentration) was prepared daily. Samples were injected in duplicate and the concentration of toluene in blood (ppm, by weight) was obtained directly from the calibration curve. The detectable limit of toluene by this method was 0.001 ppm, while the accuracy was ±0.02 ppm.

Urine Sample Collection and Analysis for Hippuric Acid:

Subjects collected 24-hr urines beginning at the start of each exposure day. The collections were made in graduated plastic jars that were placed in iced foam buckets. Each morning following the previous day's exposure, the morning urinalysis sample was added to the 24-hr

collection and the total was recorded. Samples were frozen for subsequent analyses.

Determinations of urinary creatinine, by the method found in Davidsohn and Henry[4], were carried out in order to ascertain the validity of the 24-hr urine collection.

A colorimetric method developed by Tomokuni and Agata[5] was adopted with modification for the analysis of hippuric acid, a metabolite of toluene. A Coleman Junior II A Linear Absorbance Spectrophotometer Model 6-20A was used for this determination on an aliquot of the 24-hr urine collection. One ml of urine was diluted with 4 ml of distilled water. A half ml of this diluted urine was pipetted into a glass tube, followed by 0.5 ml pyridine. The resulting solution was well mixed before introducing a 0.2-ml aliquot of benzenesulfonyl chloride (Aldrich Chemical Company). An orange color developed immediately. The colored solution was well mixed by means of gentle shaking and was allowed to stand at room temperature for 30 min. The sample was then diluted to 5 ml with 95% ethanol. The level of hippuric acid in urine was read against a 95% ethanol blank at 410 nm. At least 2 aqueous standard solutions were used to bracket the unknown concentrations. All samples were determined in duplicate with an accuracy of ± 0.05 mg/ml.

Neurological Studies:

Within 5 min of entry into the environmental chamber on each exposure day, and within 10 min prior to exit, each subject performed a modified Romberg and heel-to-toe equilibrium test which was videotaped for later inspection if necessary. The test consisted of standing upon each leg singly with arms at the side for a minimum of 3 sec, and walking heel-to-toe in a straight line for approximately 5 ft. This was first done with the eyes open and then repeated

with the eyes shut.

Spontaneous electroencephalograms (EEG) and visual evoked responses (VER) were recorded 4 times each on Monday, Wednesday, and Friday on Group I (7-1/2-hr) subjects. In addition, studies were carried out on male subjects during the afternoon of the second day of exposure to 100 ppm fluctuating (week 5, day 2) while the concentration of toluene in the chamber was 150 ppm. Recordings were normally made once during the first hr and 3 times after the 5th hr of exposure. A complete description and illustration of the EEG-VER monitoring system is found in a previous publication[6] from this laboratory. Gold-plated silver disk electrodes were oriented on the scalp according to the 10-20 International Electrode System[7]. The paste-filled disk electrode at the inion was cemented with collodion to the scalp to prevent shifting. An 8-channel Grass polygraph fitted with EEG amplifiers was utilized for recording. EEG activity was recorded for 15-30 sec before, periodically during, and 15-30 sec after acquisition of the VER. The EEG recordings were analyzed by visual examination.

The VER was recorded from the electrode at the inion, referred to the left ear. An EEG channel was used to amplify the VER, and the output was fed to an on-line averaging computer (Nuclear Chicago, 7100). The VER was triggered by a strobe flash (3 μsec) at the rate of 1 per sec for 100 sec. The strobe was operated to deliver 18 million beam candles at 1 m from the subject's eyes, which were closed throughout the period of strobe flashing. Analysis time was 250 msec. Flash delay from the synchronizing pulse which initiated the computer sweep was 25 msec. The computer averaged the response to the 100 flashes, and the resultant VER was recorded on an X-Y plotter for analysis.

It has been shown that VER amplitude can be altered by varying levels of attention, cortical desynchronization, and sleep[8,9,10]. Accordingly, standardized conditions were used throughout each exposure day, specifically immediately preceding the actual recordings. After entering the booth, the subject was always allowed 3 - 5 min to achieve a relaxed state, and then immediately prior to initiating the strobe flash, in an attempt to standardize "attention", the subject clapped his hands 5 times slowly and forcibly.

The most prominent and reproducible portions of the VER complex are the 3rd, 4th, and 5th waves (designation by Gastaut)[6,9,11]. Our analysis was thus restricted to these waves. Wave 3 was identified as proceeding in a positive direction 80 - 120 msec after initiation of the strobe flash. Waves 4 and 5 were the succeeding negative and positive segments of the VER. Our analysis involved 1) measuring the amplitude of these waves, and 2) measuring whether changes had occurred in latency and wave form of the VER complex.

Cardio-Pulmonary Function Studies:

Measurements designed to evaluate functional integrity of pulmonary airways, alveolar-capillary gas exchange, and regulation of pulmonary ventilation and heart rate were made on male Group I subjects between the 5th and 7th hours of exposure on day 4 of each exposure week. Four subjects were studied during the first 2 of these sessions while in the final 3 sessions, only 2 subjects remained in the group. Group II subjects were studied on a limited basis during 0-ppm conditions both before and after toluene exposure.

Functional integrity of airways was assessed by having the subject perform a forced maximum expiratory maneuver. The subject was seated, erect, and breathing through a mouthpiece connected with wide bore tubing to a Fleisch flow-transducer. The transducer was connected to a Vertek pneumotachograph

which sent analog data to the analog-to-digital converter of a PDP-12 computer. Appropriate software was utilized to calculate values for vital capacity (FVC), percent of VC expired in 1 sec (FEV 1), peak expiratory flow rate (PEFR), and flow rate at 50% of FVC (MMEF). This maneuver was performed at least 3 times, with the data from the 2 "best" maneuvers being saved on magnetic tape. The mean of the 2 values was taken as indicative of the function for each specific condition.

Alveolar-capillary gas exchange was assessed by the single breath carbon monoxide diffusion technique (D_LCO). Each day measurements were made twice on each subject at rest and once during the sixth min of 2 levels of moderate exercise on a bicycle ergometer [12]. The first exercise level was to elicit a heart rate of approximately 110 beats/min (350 KPM) while the second elicited a heart rate of approximately 150 beats/min (750KPM). Computerized systems as noted above were used to calculate inspired, residual, and total lung volume and D_LCO. Neon was used as the inert gas to measure residual volume. Neon and CO concentrations in the collected alveolar sample were analyzed using a Quintron Thermoconductivity Chromatograph.

Pulmonary ventilation, Pa_{CO_2}, arterial pH, Pa_{O_2}, and metabolic rate were measured directly or calculated for resting and 2 conditions of exercise (5th-6th min). These parameters were used to assess the effect of toluene exposure on mechanisms regulating breathing. Ventilation was measured using a Parkinson-Cowan gas meter whose output was fed to a Hewlitt-Packard recorder. While ventilation was being measured, 50 ml of the mixed expired air was collected in a glass syringe. This sample was analyzed for CO_2 and O_2 concentration using a Quintron chromatograph. Ventilation and CO_2 and O_2 concentration were used to calculate metabolic rate and Pa_{O_2}. For sampling

of blood, a 21-gauge needle was placed in a superficial dorsal hand vein. The needle was attached to a tubing stopcock arrangement which during non-sampling periods was filled with heparinized saline. For 5 min prior to sampling, the entire hand was heated to approximately 42° C. This procedure sufficiently "arterializes" the blood so that P_{CO_2} and pH are virtually identical to arterial[13]. The blood was analyzed within 15 min for P_{CO_2} and pH with the Radiometer electrode arrangement.

Heart rate was measured using the Biotel 170 ECG patient telemetry system developed by Spacelabs, Inc. (Chatworth, California). Heart rate was measured during the 30-sec interval preceding initiation of the exercise and over the final 30-sec interval of each exercise period (350 and 750 KPM).

Cognitive Testing:

A battery of cognitive tests was performed by the male subjects exposed for 3 and 7-1/2 hr. An alertness test lasting 1 1/2 hr was performed on days 2 and 4 of each week. It began 2 hr after the start of the 7-1/2 hr exposure and 1 hr after start of the 3-hr exposure. No training was required for this test, therefore it was also performed by the female subjects. On days 1, 3, and 5 of each week, the remaining tests in the series were performed by the male subjects beginning at 3 and 2 hr after beginning exposure for the 7-1/2 and 3-hr groups, respectively. The subjects were trained to a performance plateau before these tests were used during exposures.

The subjects sat in comfortable chairs at individual carrels to perform the cognitive tests. The subjects were not permitted to talk or have access to watches, food, soft drinks, radios, etc. during the tests. All instructional commands were made from outside of the chamber via an intercom system. The

tests are described below in the order in which they were performed.

Alertness Test: This test, called the "clock" test because the subject watches a black clock face from which all numerals and hands have been removed except the sweep second hand, was administered and graded by a PDP-12 computer. It presented a primary and secondary task. For the primary task, the subject pressed a hand-held micro-switch as rapidly as possible whenever he observed a "stop and start" of the sweep second hand. The clock stoppages were for 0.23 sec or 0.13 sec, occurring 30 times during the 90-min test. For the secondary task, the subject pressed the hand-held switch whenever a tone was heard through the headphones he was wearing. These auditory signals were presented randomly for 1 sec, 3 to 6 times per test. At the completion of the test, the computer printed the results in table form for each subject. The table listed signal duration, time of occurrence, reaction time or miss for each signal, percent correct for the day, and the average reaction times for clock stoppages and for tones.

Ten- and Thirty-Second Time Estimation Test: Each male subject upon verbal signal "ready, begin", depressed a hand-held, silent, push-button micro-switch for an interval of time he estimated to be 10 sec. This was repeated 2 additional times, and then 3 30-sec estimates were made. The micro-switches were connected to a polygraph whose pen-deflection could be read to the closest 10 msec. This test took approximately 3 min to perform.

Marquette Time Estimation Test: This test consisted of a series of 9 tone stimuli followed by 9 light stimuli of approximately 1, 3 or 5 sec duration presented in a random sequence but always with 3 stimuli of each time interval. At the termination of each stimulus, the subject depressed the push button for that interval of time he estimated to be equal in length to the original auditory or light stimulus. A detailed description of the test and

the instrumentation used to carry it out has been described by Stewart, et al [14]. This test took approximately 7 min to perform.

Coordination Test: This test was the Flanagan Aptitude Classification Tests, 7A, Coordination, published by Science Research Associates, Inc., 259 East Erie Street, Chicago, Illinois. This test asked the subject to rapidly follow a spiral pathway with a pencil. The subject was allowed 40 sec to complete each of 6 spirals. The first 2 were considered practice and the last 4 were scored and totaled. The total score depended upon the longest distance attained in each spiral minus the number of times the sides of the spiral pathway were touched with the pencil. This test took approximately 5 min to perform.

Arithmetic Test: This test, which measured the subjects' ability to work with numbers, was divided into 2 parts. The first part, lasting 5 min, consisted of simple addition and subtraction problems while the second part, lasting 3 min, consisted of multiplication and division. The maximum score attainable if all answers were correct was 125; however, no subject completed the tests in the allotted time. In order to minimize memorization of answers, 4 permutations of problem order were used.

Inspection Test: This test was a measure of the subject's ability to spot the number "3" in rows of random numbers on an 8-1/2" x 11" page. The subject was asked to scan each row, beginning at the top of the page, and slash out with a red pencil each "3" encountered. The subject was given 2 min to strike out as many as possible. No subject ever finished the entire page. A subject's score was the total number of "3's" struck. Six differing pages with random numbers were utilized so that no subject received an identical number sheet on successive tests.

Other Studies:

Subjective Responses: Each subject was asked to note on an individualized form any subjective responses occurring during the exposure in the chamber or during the first 3 hr post-exposure. The form contained rows for noting headache, nausea, dizziness, abdominal pain, eye, nose, throat irritation, other, and odor, and columns for the "immediate", "1/2-hr", and hourly periods of time thereafter. The adjectives "mild, moderate, and strong" appeared on the sheet as cue words, and the phrase "only abnormalities recorded" was prominently typed at the bottom. Each of the Department physicians' home telephone number appeared on the form and the subjects were encouraged to phone if they became ill while away from the laboratory.

The physicians and staff made a special effort to determine the effect of exposure to toluene on appetite changes and sleep requirements of the subjects. Each subject was specifically queried regarding these subjective areas in the A.M. following exposure. Each male subject was also queried on at least 2 Saturday mornings regarding the odor of toluene, specifically "was it pleasant or unpleasant?" Female subjects were queried one Saturday morning.

Breath Containers: Breath containers, either Saran bags (4-5ℓ), glass tubes (approx. 50 ml), or plastic soft drink type bottles (Dow, approx. 400 ml), were flushed with chamber air while the concentration of toluene in the controlled environment chamber was held at approximately 50 ppm. Analyses for toluene concentration in representative containers were carried out immediately after filling and 24, 72 and 120 hr later. One Saran bag and 5 glass tubes were mailed to the laboratory from approximately 50 miles distant and analyzed at the 120-hr period.

All analyses were carried out by the GC method previously described for analyzing breath samples for toluene.

Because toluene is slightly soluble in water (47 mg/100 ml at 16° C), and a few drops of water often collect in the Saran bags used for breath containers, 2 sets of 2 standards containing either 9.3 or 18.7 ppm toluene were prepared. In one set, 1 ml of water was added to each bag and the bags were allowed to equilibrate for 1 hr at room temperature prior to analysis of all bags by GC.

RESULTS

Analysis of Exposure Chamber Atmosphere:

The daily time-weighted average (TWA) concentrations of toluene vapor in the environmental chamber for each group of subjects are found in Table II. Also listed are the numbers of subjects participating in each group. Actual TWA concentrations were generally very close to those desired with the exception of week 3, day 3, male subjects, when the chamber operator had difficulty with damper controls and ended with a lower than desirable concentration. On day 2, week 5, Group I male subjects were purposely exposed to approximately 150 ppm during the last 3-1/2 hr of exposure, giving these 2 subjects a TWA exposure concentration of 118 ppm. All other TWA exposures were within a few percent of those desired.

Medical Surveillance:

Pre- and post-exposure comprehensive medical examinations revealed that all subjects were in good health before and after the study. The attached forms (History - Appendix II, Physical Examination - Appendix III) were used and are retained in each subject's personal file. Blood clinical chemistries

obtained before, during, and after the study revealed no unusual abnormalities. Included in the blood clinical chemistries obtained during the study of male subjects were glucose, urea nitrogen (BUN), uric acid, total protein, albumin, total bilirubin, alkaline phosphatase, and SGOT. For the pre-exposure samples, calcium, inorganic phosphorous, cholesterol, SGPT, and protein bound iodine (PBI) were added to the list, and post-exposure creatinine, BUN/creatinine ratio, albumin/globulin ratio, thymol turbidity, direct bilirubin, lactic acid dehydrogenase (LDH), amylase, beta lipids, total lipid, sodium, potassium, chloride, and gamma-glutamyl trans-peptidase were added, while PBI was not run. The profile for female subjects included those clinical chemistries that were included in the post-exposure male studies. No female subjects became pregnant during the period of time they were in the study. All daily urinalysis tests were within normal color ranges (Combistix: glucose, blood, protein, pH).

Complete blood count studies included white blood cells (WBC), red blood cells (RBC), hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, differential count, and platelet adequacy. Of special importance were the WBC and RBC values and platelet adequacy. For female subjects these parameters were all within normal limits, while for males the RBC values and platelet adequacy were all within the normal range of the laboratory. Table III lists the WBC values for each male subject. As seen in the Table, 4/10 males had low WBCs before being exposed to toluene (pre-exposure and/or after 1 day at 0 ppm), 3 continued with abnormally

low values during subsequent exposures to toluene, but only 1 continued to have a low abnormal value on his post-exposure physical. This subject also had a low WBC on his pre-exposure physical. Out-of-normal range values for other serology parameters were also of no significance.

During the second day of exposure of male subjects to a 100 ppm fluctuating concentration of toluene (week 5), one 7-1/2-hr subject complained to the physician of pain and stuffiness of the right nostril. Examination of this subject, the other 7-1/2-hr subject, and a 3-hr subject revealed the following:

"-Subject 203 (7-1/2 hr) complains of pain and stuffiness of right nostril. Clinical examination discloses a very red and painful mucosa with the nostril practically closed up. Examination of left nostril shows red mucosa, not so much pain. Both nostrils have a slight purulent exudate.

-Subject 169 (7-1/2 hr) does not complain of any subjective feeling. Clinical examination shows that the mucosa of both nostrils is heavily injected and there is a small amount of purulent exudate. Airways are still open.

-Subject 207 (3 hr) is complaining of a sore throat. Clinical examination shows injection of the nose mucosa and irritation of the pharynx."

It was decided to conclude exposures to >0 ppm toluene vapor on that day. Approximately 3 days later, when post-exposure physical examinations were conducted, the above 3 subjects showed complete recovery of mucosal membranes. None of the female subjects, who were exposed to 100 ppm toluene vapor for 5 days, exhibited mucosal irritation.

Several of the subjects, particularly the males, experienced common cold symptoms. This period of the year no doubt contributed to the rather large number of absences (see Table II). One 7-1/2-hr subject dropped out of the study after week 2 due to illness not associated with the exposure. The other drop-out from this group occurred when the subject obtained a higher paying job. One of the 1-hr subjects dropped out of the study at the end of week 4 due to outside job pressures. He was replaced during the last week with a faculty member.

There was no problem with large consumption of alcohol during the study. Several subjects reported mild to moderate consumption of alcohol at home after all daily breath samples were completed, but none were excessive. The use of common cold preparations was higher than normally experienced during this type of study. One male subject was on daily ataractic medication. Use of other drugs was almost non-existent.

Breath Analysis:

Analysis of breath samples was carried out on the same day that the samples were given, with the exception of the 2- and 3-hr post-exposure samples which were given after the subjects left the laboratory and thus were analyzed the following day. All samples were collected in Saran

bags, which were generally leak-proof, but occasionally developed pin-holes or slits. A potential source of error in the take-home bags could occur if a subject forgot to give the sample at the prescribed time. In determining the mean value and standard deviation for the concentration of toluene in the alveolar breath samples, any value that was obviously in error was discarded. Approximately 8% of the values were discarded from the week 2, male, exposures and approximately 6% from the remainder. The mean values and one standard deviation are given in Tables IV, V and VI for male subjects, while for female subjects these values are found in Tables VII, VIII, and IX. Where no standard deviation is listed, the value represents a single value.

Alveolar breath samples collected from each female subject 15 min post-exposure after exposure to 100 ppm toluene were slow-scanned in the infrared spectrophotometer. No unusual absorption changes from a control breath sample were seen.

Analysis of Toluene in Blood:

Blood samples from subjects exposed to toluene were assayed for this chemical pre-exposure, immediately before completing the designated exposure, and 15 min post-exposure on Monday and Friday of each exposure week. There was no toluene found (<0.001 ppm) in Friday samples taken before any exposure to toluene occurred, neither was there any in blood samples taken Monday or Friday following the last exposure to toluene. The results of the individual analysis of all samples taken during the exposure weeks are given in Tables X to XIII.

After the first exposure day of male subjects to 20 ppm toluene,

there was no toluene found in the blood of the 7-1/2-hr subjects. After four days of exposure to this level, the 1-hr subjects' blood contained <0.001 ppm, the 3-hr subjects averaged 0.26 ppm, while the 7-1/2-hr averaged 0.44 ppm. After 1 day of exposure to 50 ppm, the 1-hr subjects averaged 2.00 ppm, the 3-hr 1.64 ppm, and the 7-1/2-hr 1.75 ppm. Exposure to 100 ppm toluene, steady or fluctuating, resulted in similar blood levels after 1 day and after 5 days. Averaging all results for the 1-hr exposures, the male value was 2.88 (n=6) and the female was 2.51 ppm (n=4), while after 3 hr of exposure the male average value was 3.80 (n=12) and the female was 2.88 ppm (n=8), and after 7-1/2 hr of exposure the male average value was 3.32 (n=6) and the female was 3.36 ppm (n=8).

Analysis of Hippuric Acid in Urine:

Aliquots of 24-hr urine collections were assayed for hippuric acid, a metabolite of toluene, and for creatinine as a measure of the validity of a 24-hr collection. The lower limit of normal for 24-hr total urinary creatinine excretion by the method used was 1.0 g for males and 0.8 g for females. All of a subject's 24-hr creatinine values above the lower limits were used to determine the mean value for that subject, and that mean value was then used to determine a corrected 24-hr urine volume for any below-normal days. Corrected urine volumes were then used to determine daily hippuric acid excretion. The mean values, standard deviations, and the ranges are listed for each Group at each toluene exposure concentration in Table XIV. Mean values were generally higher after exposure to higher concentrations of toluene, but the ranges always overlapped the control range.

Neurological Studies:

The modified Romberg and heel-to-to test was used as a subjective measure of the subjects' equilibrium when entering and exiting the chamber. A minus sign was recorded by the observer when a subject was unable to maintain equilibrium during the 15 to 20 sec it took to perform these simple maneuvers. A loss of equilibrium occurred in 5 subjects during zero exposure (4 upon entry and 1 upon exit), while this was noted in 4 subjects (2 upon entry and 2 upon exit) during days of exposure to >0 ppm toluene. All occurred in male subjects, with eyes closed. There was no relationship to exposure concentration because 7 of the 9 occurred either during zero exposures or immediately upon entry into the chamber.

The spontaneous EEG, measured on Monday, Wednesday and Friday of each week, remained unaltered for 2 male subjects (#169 and #203) during exposures to 20, 100, 50, and 100 (fluctuating) ppm toluene. A representative EEG for subject #169 at each concentration is illustrated in Figures 2 and 3. These figures demonstrate excellent agreement with control (0 ppm) in frequency, amplitude and overall wave configuration. Similarly, for the 4 female subjects (#178, #211, #212, and #213), the spontaneous EEG was unaltered from control during a one-week exposure to 100 ppm of toluene. Figure 4 shows the unaltered EEG of female subject #178 for 5 days of exposure to 100 ppm.

The results for the VER measurements are somewhat limited because only 2 subjects participated in this phase of the study. Figures 5 and 6 show a typical VER wave configuration during each exposure condition for subjects #169 and #203, respectively. Examination of Figure 5

for subject #169 shows an increase in VER amplitude at 100 ppm on Friday followed by a return to normal at 0 ppm. There is a decrease in amplitude at 100 ppm, fluctuating, followed by a further decrease on the following day at 150 ppm. The amplitude then returned to pre-exposure values during the 2 days at 0 ppm. Table XV, which lists F and paired-t values compared to pre-exposure contols, verifies these trends of amplitude change at 100 ppm and 150 ppm to be a statistically significant increase and decrease, respectively. Subject #203 did not demonstrate the same trend. This subject, however, did show considerable variability in waves 4 and 5 as seen by the significant F values in Table XV.

The 4 female subjects did not demonstrate statistically significant trends in their VERs during exposures to 100 ppm of toluene. Figure 7 illustrates representative VERs for subject #178. The amplitude and configuration remained uniform during the study. Measurements on 100-ppm exposure days and the final 0-ppm exposure day were compared to those obtained on the 0-ppm exposure day prior to any exposure to toluene vapors and no consistent differences were found.

Cardio-Pulmonary Function Studies:

The results of the cardio-pulmonary function studies on males are listed in Tables XVI-XIX. In Table XVI, individual values for Group I and mean values for Group II subjects are shown for variables used to evaluate the functional integrity of the pulmonary airways. The data indicate that there were no changes during exposure to toluene. The same deduction can be made from the data in Tables XVII, XVIII, and XIX, which contain the mean values obtained for parameters used to evaluate the

regulation of ventilation, heart rate, and alveolar-capillary gas exchange at rest and at 2 separate work loads for Group I subjects.

Cognitive Testing:

Cognitive testing, with the exception of the alertness test, was carried out by male subjects only, on Monday, Wednesday and Friday of each week. Figures 8-27 show the effect of training and exposure to toluene on the cognitive tests for Groups I and II. Similarly, Figures 28-47 show test performance versus exposure concentration and Tables XX and XXI present paired-t values for exposure versus control test performance. The data in these figures and tables show no significant effect of toluene at these exposure levels on cognitive test performance. There are no apparent dose related trends and any significant t values appear to be spurious.

The results of the paired-t test comparison of alertness performance during and before toluene exposures are listed in Table XXII for male and Table XXIII for female subjects. Other than spurious differences probably occurred during the exposure of females to 100 ppm toluene. On both Wednesday and Friday, female subjects had significantly fewer correct responses than they did prior to the week's exposure.

Subjective Responses:

All subjects perceived a mild to strong odor immediately upon entering the chamber at all times that toluene vapors actually existed in the environmental chamber, whether the concentration of toluene was 20, 50, or 100 ppm. Most subjects lost their ability to detect the odor after 1/2 to 3 - 4 hr, depending somewhat upon concentration. However, this

acclimatization to odor was highly individualistic. When questioned by a physician at week's end regarding the type of odor noted, 12 responses were "pleasant", 7 were plus-minus, and 8 answered that it was "unpleasant".

There was essentially no change in the subjects' appetite or sleep requirements during any part of the study.

Subjective responses as noted by the subjects on forms supplied to them during each exposure are summarized on Table XXIV. The number of subject-days records the total number of forms returned by all subjects exposed for an identical period of time. The 100 ppm column contains results from both 100 ppm (steady) and 100 ppm (fluctuating) exposures. The most prevalent complaint during 0 ppm exposures was "headache", the next was "eye, nose and/or throat irritation", and finally "other". No assessment of the degree or duration of these responses was attempted. In perusing the table, it was obvious that the 3-hr subjects complained more than usual of ENT irritation during 100-ppm exposures. It was calculated that these occurred 3 times as often as expected from the control exposures. There was no difference for the 7-1/2-hr subjects, nor the 1-hr subjects, between 0-ppm exposures and >0-ppm exposures.

Breath Containers:

Table XXV lists the results of the breath container study. Although very unusual, 2 of the 4 Saran bags proved to be leakers over the 120-hr period. The Saran bag, sent through the mail with the glass tubes, also leaked. This was not surprising because Saran film tends to become brittle and crack when it becomes cold. All 3 types of containers

retained the toluene vapor quite well, with a 10 to 20% loss in concentration by 24 hr.

The concentration of toluene vapor in Saran bags containing 1 ml of water was approximately 10% below that found in dry bags at 10 and 20 ppm.

DISCUSSION

Approximately a billion gallons of toluene will be produced in the U.S. in 1975[15], placing this aromatic intermediate and solvent high on the list of the top 50 chemicals by tonnage. Because it appears as both an intermediate and solvent in chemical manufacture and as a solvent for commercial products, the total population is the potential recipient of exposure to its vapors. The TLV for the industrial worker was 200 ppm until 1971 when 100 ppm was adopted by the ACGIH[16]. Gerarde[17] in 1960 reported that the threshold limit in the U.S.S.R. at that time was 25 ppm, and that the then TLV of 200 ppm in the U.S. appeared to be excessive. Von Oettingen et al[18] had reported human studies in 1942 that revealed rather severe subjective responses (insomnia, incoordination, parethesia, nausea, confusion, weakness) at an exposure level of 200 ppm for eight hours. These responses were reduced to fatigue and sleepiness at 100 ppm, and drowsiness and headache at 50 ppm. Toluene blood levels at these two lower exposure levels can be estimated from the graph produced by Gerarde[17] to have been below five ppm.

Only limited human studies at the TLV levels of vapor exposure have been reported since Gerarde's monograph. The most important are

the two papers from Sweden[1,2] referred to earlier. In the first of these two papers, studies on toluene at the National Board of Occupational Safety and Health, Stockholm, Sweden, revealed that exercise increased the venous, arterial, and alveolar concentrations of toluene several fold over sedentary levels. The authors found no effect on the subjects' cardiopulmonary functions from their limited exposures (longest time of exposure was 130 minutes, highest exposure concentration was 200 ppm). Although they denigrated the use of post-exposure breath analysis, they suggested that "[t]he results support the view that customary threshold limit values should be complemented by biological limit values which are established at levels permitting the performance of light work without limit value exceeding." In the second paper from this group, "psychophysiological functions" were assessed in subjects exposed sequentially to increasing toluene vapor concentrations for thirty-minute intervals. Only simple reaction time was impaired at 300 ppm, while there was no impairment in the perceptual speed: identical numbers, perceptual speed: spokes, simple reaction time, and choice reaction time tests at 100 ppm. Unfortunately, none of the data appear applicable to an eight hours per day, five days per week, work situation.

Our studies were designed to elicit responses and effects under <u>simulated</u> sedentary working conditions. The effects seen and the biologic results obtained should be confirmed under <u>actual</u> sedentary and non-sedentary working conditions. It is predictable that the questionable deleterious effects seen at 100 ppm under sedentary conditions will be exacerbated in non-sedentary workers.

The health of our subjects remained unimpaired during these studies. The blood clinical chemistries, serologies, urinalyses, electrocardiograms, electroencephalograms, mechanisms regulating ventilation and heart rate, and mechanisms regulating alveolar-capillary gas exchange, all remained normal or did not vary significantly from pre-exposure values during exposures to toluene.

Cognitive task testing revealed a potential effect on the 7-1/2-hr female subjects ability to concentrate on the alertness test, a boring task requiring alertness for a long period of time. This was revealed by a significant decrement on Wednesday and Friday at an exposure concentration of 100 ppm in the percent of correct responses on the alertness test when compared to the first control day. However, this decrement was not observed in male subjects, or in the 3-hr females. Therefore it cannot be concluded without additional testing that the deleterious effect was real, because this test is highly dependent upon motivation. There were no other significant decrements in cognitive testing at 100 ppm or lower, which agrees with the work of the Swedish group[2].

The neurological testing also revealed a potentially deleterious effect of exposure to 100 ppm of toluene vapor for 7-1/2 hr per day. One of two male subjects exhibited a significant increase in the amplitude of the visual evoked response on the fifth day of exposure, suggesting a depression or synchronization of cerebral cortical activity. The significant reduction in VER amplitude the next week while being exposed to 150 ppm toluene suggests possible cortical excitation or desynchronization. These changes could be interpreted as resulting from

a pre-narcosis response[10]. However, interpretation of changes in VERs is still open to question, and because none of the four female subjects or the other male subject exhibited significant VER changes, this finding must also be considered a tentative deleterious effect that must be verified with further studies.

The third area of response wherein a deleterious effect was found was that of subjective responses. Eye, nose and/or throat irritation responses were increased approximately threefold in both the female and male subjects that were exposed for 3 hr to 100 ppm. Surprisingly, the 7-1/2 hr group did not note a similar increased irritation of soft tissue. The rationale for this deleterious response solely in the group exposed for a shorter period of time is difficult. It is probably related to individual levels of sensitivity. The nostrils of both 7-1/2-hr male subjects were inflamed and injected on the last day of exposure, but only one of them marked the response as ENT irritation. The finding of increased soft tissue irritation at an exposure level of 100 ppm agrees with published reports[3]. However, our study did not reveal an increase in drowsiness, fatigue, sleepiness or headache at this level, as reported for the small group of subjects studied by Von Oettingen, et al[18]. We also saw no decrease in subjects' appetites, and only one complaint of insomnia from twenty subjects.

A study of the subjective responses with regard to odor confirms Gerarde's[17] statement that "no reliance can be placed on the sensory responses as a warning of dangerous concentrations." Although all subjects could immediately detect the odor when toluene vapors were present, many subjects lost their ability to detect it during their

sojourn in the chamber, and all indicated some diminution of odor intensity even though the concentration remained steady.

Venous blood levels of toluene agreed very well with those predicted for these lower levels of exposure from the graph in Gerarde's monograph[17]. Blood levels were generally equivalent after one, three, or 7-1/2 hours of exposure to 50 or 100 ppm, but increased with increasing exposure time at 20 ppm. Comparison with the work of Åstrand, et al[1] is difficult because of differing exposure times, exercise, and the small graphs in their publication. They also found a rather steady venous blood concentration of toluene while subjects were at rest, or after 30 min of exercise. Although blood analysis may be a valid indicator of toluene body burden, the difficulty of obtaining multiple samples and of assay preclude its general use for estimating the magnitude of a toluene exposure.

Many papers have appeared regarding the excretion of urinary hippuric acid during toluene exposures. Our studies confirmed these reports which generally have concluded that other dietary precursors of hippuric acid preclude the use of monitoring toluene exposure by this measurement[3]. In all subjects the 24-hr excretion remained below 5g of hippuric acid. There was considerable overlap of total excretion between the four exposure concentrations.

The analysis of toluene in the alveolar breath has allowed us to construct the breath analysis decay curves (BADC) shown in Figures 48, 49, and 50. Before discussing these data, several interesting points should be made. The first is that a perusal of the tables containing daily means (Tables IV-IX) reveals that immediately upon exit

from the chamber, the alveolar breath samples contained a concentration of toluene equal to 10-20% of the atmospheric concentration of toluene in the chamber, no matter how long the exposure. This means that approximately 80% of the toluene vapor in the alveolar spaces was absorbed systemically at all times. With rather constant blood levels at 1, 3 or 7-1/2 hours of exposure to the same concentration of toluene, it can be concluded that the total body intake of toluene must be greater for the 7-1/2-hr exposure than for the 3-hr, which must be greater than for the 1-hr. There are then two known routes for the toluene molecule in the body during exposure, metabolism and tissue storage. We believe that the increased area under the 7-1/2-hr breath decay curve, when compared to a 3-hr or 1-hr breath decay curve, represents that additional tissue storage of unmetabolized toluene which results from longer exposures. This explains the rationale for the relationship of the BADC to magnitude of exposure.

Another point of interest is that, although there was a small amount of toluene in the breath of all subjects the morning after an exposure, it was insufficient to cause a general increase in breath levels upon consecutive daily exposure. Considerable daily variation of mean toluene breath concentrations did occur after exposure to the same concentrations of toluene for an identical time period, particularly during the early post-exposure period. In addition, there was considerable overlap of values between the 1-hr and 3-hr subjects. From the data it appears that breath samples for determining the magnitude of an exposure (concentration multiplied by time) are best obtained at one to three hours post-exposure. This is confirmed by the breath analysis

decay curves (BADC) found in Figures 48 and 49. Figure 50 demonstrates the BADC for the 7-1/2 hr sedentary exposure of males and females to 100 ppm toluene, the present TLV. It is our opinion that this BADC, with an upper limit of range values, can be used as the "biologic threshold limit value" for toluene. Although the TLV of 100 ppm for toluene was primarily based on the irritation of soft tissues at 200 ppm, there is sufficient suggestive evidence in our studies indicating a systemic deleterious effect at levels near 100 ppm, and therefore the margin of safety at 100 ppm for sedentary workers is probably only two to three-fold. This margin of safety will be reduced for those workers who are physically active.

CONCLUSIONS

Healthy adults of both sexes were exposed to vapor concentrations of toluene in the environmentally controlled chamber that simulated sedentary work place exposures at the 1971 TLV and two lower concentrations. Control exposures to zero concentration of the chemical were carried out before, during, and after the toluene exposures. Exposure to toluene at 100 ppm for 7-1/2 hours per day, five days per week, resulted in unproven but provocatively suggestive deleterious effects. These included an effect on the visual evoked response of one subject, a significant increase in errors by female subjects carrying out an alertness test, and irritation of the nasal mucosa of two male subjects. In addition, both male and female groups of subjects exposed for three hours per day noted an increase in eye, nose, and/or throat irritation.

Toluene venous blood levels remained fairly constant with time for exposures at levels of 50 or 100 ppm, and excretion of the toluene metabolite, hippuric acid, increased with toluene exposure. However, neither of these parameters qualified as a biologic standard. The "biologic threshold limit value" for workers exposed to toluene is suggested to be the upper limit of the range of the breath analysis decay curve developed from subjects exposed to toluene vapors for 7-1/2 hours per day for five days.

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BIBLIOGRAPHY

1. Åstrand, I., Ehrner-Samuel, H., Kilbom, Å., Övrum, P., Toluene Exposure I. Concentration in Alveolar Air and Blood at Rest and During Exercise, Work-environm.-hlth. 9:119-130, 1972.

2. Gamberale, F., Hultengren, M., Toluene Exposure II. Psychophysiological Functions, Work-environm.-hlth. 9:131-139, 1972.

3. Excerpts from, Criteria For a Recommended Standard ... Occupational Exposure to Toluene, and Commentary by Weaver, N.K., J. Occup. Med. 16:107-111, 1974.

4. Davidsohn, I., Henry, J.B., Todd-Sanford Clinical Diagnosis by Laboratory Methods, 14th Ed., W.B. Saunders, Co., Philadelphia, 1969, p. 545.

5. Tomokuni, K., Ogata, M., Direct Colorimetric Determinations of Hippuric Acids and Methyl Hippuric Acids, Metabolites of Toluene and Xylene in the Urine, Jap. J. Ind. Health 14:103-107, 1972. (Abstract: Ind. Hyg. Digest Sept 1972, p. 15.)

6. Hosko, M.J., The Effect of Carbon Monoxide on the Visual Evoked Response in Man, Arch. Environ. Health 21:174-180, 1970.

7. Jasper, H.H., The 10-20 Electrode Systems of the International Federation, EEG Clin. Neurophysiol. 10:371-375, 1958.

8. Bergamasco, B., Excitability Cycle of the Visual Cortex in Normal Subjects During Phychosensory Rest and Cardiovolic Activation. Brain Res. 2:51-60, 1966.

BIBLIOGRAPHY (Cont'd.)

9. Gastaut, H., Regis, H., Visually Evoked Potentials Recorded Transcranially in Man, in Procter, L.D., Adez, W.R. (eds.): Symposium on the Analysis of CNS and CU Data Using Computer Methods, publication SP-72, National Aeronautics and Space Administration, Washington, D.C., 1964.

10. Perry, N.W., Childers, D.G., The Human Visual Evoked Response, C.C. Thomas, Springfield, Ill., 1969.

11. Ciganek, L., A Comparative Study of Visual, Auditory, and Comatosensory EEG Responses in Man, Exp. Brain Res. 4:118-125, 1967.

12. Forster, R.E. Diffusion of Gases. Handbook of Physiology, Sec. 3, Vol. 1. American Physiological Society, Washington, D.C., 1964, pp. 839-872.

13. Forster, H.V., Dempsey, J.A., Thomson, J., Vidruk, E., do Pico G.A., Estimation of Arterial P_{O_2}, P_{CO_2}, pH, and Lactate from Arterialized Venous Blood, J. Appl. Physiol. 32:134-137, 1972.

14. Stewart, R.D., Peterson, J.E., Baretta, E.D., Bachand, R.T., Hosko, M.J., Herrmann, A.A., Experimental Human Exposure to Carbon Monoxide, Arch. Environ. Health 21:154-164, 1970.

15. Chem. Eng. News p. 20, Dec. 23, 1974.

16. Threshold Limit Values for Substances in Workroom Air Adopted by ACGIH for 1971, Cincinnati, Ohio.

BIBLIOGRAPHY (Cont'd.)

17. Gerarde, H.W., Toxicology and Biochemistry of Aromatic Hydrocarbons, Elsevier Publishing Co., New York, 1960, pp. 141-150.

18. Von Oettingen, W.F., Neal, P.A., Donahue, D.D., The Toxicology and Potential Dangers of Toluene, J. Am. Med. Assoc. 118:579-584, 1942.

TABLE I

TOLUENE EXPOSURE SCHEDULE

MALES

Week	Days	Concentration ppm	Comment
1	4,5	0	Control
2	*,2,3,4,5	20	Steady
3	1,2,3,4,5	100	Steady
4	1,2,3	50	Steady
	4,5	0	Control
5	1,2	100	Fluctuating (50-150 ppm)
	3,4,5	0	Control
	FEMALES		
1	5	0	Control
2	1,2,3,4,5	100	Steady
3	1	0	Control

*No exposure due to monitoring difficulties.

TABLE II

TOLUENE TIME-WEIGHTED AVERAGE (TWA) EXPOSURE CONCENTRATIONS

TWA (±S.D.) in PPM

Week	Day	Scheduled Concen.	No. of Subjects	Group I 7 1/2 Hr	No. of Subjects	Group II 3 Hr	No. of Subjects	Group III 1 Hr
				MALES				
1	4	0	4	0	4	0	2	0
	5	0	4	0	4	0	2	0
2	2	20	3	18.1 (0.7)	4	18.2 (0.5)	2	18.6 (0.7)
	3	20	4	20.0 (0.9)	3	20.0 (0.8)	2	18.9 (0.8)
	4	20	4	20.0 (0.7)	3	20.2 (0.6)	2	20.2 (1.0)
	5	20	4	20.0 (0.9)	4	20.0 (0.7)	2	19.8 (0.4)
3	1	100	2	100.2 (6.6)	4	102.5 (4.7)	2	99.2 (10.2)
	2	100	2	99.6 (3.6)	4	98.6 (3.9)	2	101.0 (5.2)
	3	100	2	86.4 (4.3)	4	87.1 (5.3)	2	86.7 (4.7)
	4	100	2	101.0 (3.7)	3	100.8 (3.6)	2	103.0 (3.4)
	5	100	2	100.8 (4.1)	4	101.0 (2.9)	2	101.8 (4.6)
4	1	50	2	49.4 (2.1)	3	48.9 (2.4)	2	49.1 (1.9)
	2	50	2	50.7 (1.7)	4	50.6 (1.8)	2	50.6 (2.1)
	3	50	2	49.9 (2.0)	4	50.1 (1.2)	2	50.6 (1.6)
	4	0	2	0	4	0	2	0
	5	0	2	0	4	0	2	0
5	1	100	2	100.0 (38)	4	101.3 (39)	2	96.4 (38)
	2	100	2	118.3 (36)	3	96.3 (36)	2	97.7 (38)
	3	0	2	0	4	0	2	0
	4	0	2	0	4	0	2	0
	5	0	2	0	4	0	2	0
				FEMALES				
1	5	0	4	0	4	0	2	0
2	1	100	4	98.8 (3.0)	4	98.8 (3.0)	2	97.2 (2.8)
	2	100	4	99.9 (2.4)	4	100.0 (2.6)	2	99.1 (2.8)
	3	100	4	98.6 (2.9)	4	99.0 (2.5)	2	98.3 (3.5)
	4	100	4	99.0 (2.4)	4	99.6 (2.4)	2	100.0 (2.0)
	5	100	4	99.5 (2.0)	4	99.4 (2.0)	2	99.4 (2.3)
3	1	0	4	0	4	0	2	0

TABLE III

WBC OF MALE SUBJECTS EXPOSED TO TOLUENE

Subject No.	Pre-Exp. Physical	WEEK 1 After 1 Day at 0 ppm	WEEK 2 After 3 Days at 20 ppm	WEEK 3 After 4 days at 100 ppm	WEEK 4 After 3 Days at 50 ppm	Post-Exp. Week 5 Day 5
			GROUP I - 7 1/2 Hr			
169	6.9	4.3*	3.3*	4.1*	4.7*	5.1
202	6.1	8.2	6.9	(dropped out)		
203	5.3	6.3	6.1	5.9	5.1	5.7
204	7.7	8.4	9.5	(dropped out)		
			GROUP II - 3 Hr			
205	4.3*	5.0	4.2*	4.3*	3.7*	4.7*
206	6.3	6.6	7.0	6.4	7.5	7.5
207	6.3	3.9*	5.1	4.1*	4.5*	5.7
208	6.2	5.8	6.7	5.9	5.8	6.2
			GROUP III - 1 Hr			
209	7.1	4.7*	5.4	7.5	5.8	6.0
210	6.3	6.3	7.8	5.3	6.5	-

*Below the normal range of 4.8 - 10.8 thousand.

TABLE IV

TOLUENE CONCENTRATION IN ALVEOLAR BREATH, IN PPM (±SD)

GROUP I MALE SUBJECTS

Exposure Time: 7-1/2 Hr

Week	Day	No. of Subjects	Baseline	Immediate Exit	5 Min Post	15 Min Post	30 Min Post	1 Hr Post	2 Hr Post	3 Hr Post
				Chamber Concentration: 20 ppm (Steady)						
2	2	3	0	2.27 ±0.15	1.10 ±0.35	0.86 ±0.07	0.63 ±0.16	0.45 ±0.03	0.34	0.35 ±0.06
2	3	4	0.14 ±0.05	3.91 ±0.61	1.54 ±0.39	1.21 ±0.27	0.85 ±0.11	0.70 ±0.09	0.29	N.A.
2	4	4	Data unavailable for this day (N.A.)						0.37 ±0.35	0.25 ±0.06
2	5	4	0.17 ±0.05	2.66 ±0.45	1.24 ±0.22	0.96 ±0.14	0.69 ±0.09	0.53 ±0.12	0.57 ±0.20	0.49 ±0.07
				Chamber Concentration: 100 ppm (Steady)						
3	1	2	0	20.26 ±1.35	9.39 ±0.53	5.14 ±0.23	3.71	3.34 ±0.23	1.99	1.36 ±0.64
3	2	2	0.54 ±0.00	17.51 ±3.85	7.33 ±0.89	4.87 ±0.81	3.29 ±0.18	3.22 ±0.81	1.66 ±0.63	N.A.
3	3	2	0.56 ±0.23	14.11 ±0.81	7.01 ±0.46	4.08	3.26 ±0.00	3.06 ±0.29	2.38 ±0.13	1.96
3	4	2	0.82 ±0.08	17.19 ±3.15	6.64 ±0.71	5.36 ±0.32	3.85 ±0.24	3.74 ±0.08	2.16 ±0.00	1.35
3	5	2	0.63 ±0.30	27.09 ±2.63	11.85 ±1.86	8.71 ±0.60	6.81 ±1.32	N.A.	2.50 ±0.03	1.81
		16 hr post	0.71 ±0.19							

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TABLE IV (Continued)

TOLUENE CONCENTRATION IN ALVEOLAR BREATH, IN PPM (±SD)

GROUP I MALE SUBJECTS

Exposure Time: 7-1/2 Hr

Week	Day	No. of Subjects	Baseline	Immediate Exit	5 Min Post	15 Min Post	30 Min Post	1 Hr Post	2 Hr Post	3 Hr Post
				Chamber Concentration: 50 ppm (Steady)						
4	1	2	0.24 ±0.04	8.94 ±0.79	3.85 ±0.42	2.65 ±0.00	2.18 ±0.15	1.38 ±0.00	0.91	0.68
4	2	2	0.34 ±0.16	8.56 ±0.33	3.26 ±0.40	2.45 ±0.57	1.55 ±0.40	1.43 ±0.73	1.03	0.70 ±0.07
4	3	2	0.70 ±0.20	7.56 ±2.38	3.31 ±0.72	2.15 ±0.66	1.64 ±0.33	N.A.	1.55 ±0.35	1.20 ±0.14
4	4	2	0.75 ±0.00	No Samples Run -- "Zero" Exposure						
				Chamber Concentration: 100 ppm (Fluctuating)						
5	1	2	0.22	16.50 ±1.05	5.63 ±0.00	4.08 ±0.74	2.70 ±0.08	2.41 ±0.33	1.61	0.89 ±0.04
5	2	2	0.56 ±0.22	19.72 ±5.16	8.88 ±2.37	5.28 ±0.49	4.78 ±0.91	3.60 ±1.47	2.49 ±0.92	2.02 ±0.15
5	3	2	0.96 ±0.00	No Samples Run -- "Zero" Exposure						

TABLE V

TOLUENE CONCENTRATION IN ALVEOLAR BREATH, IN PPM (±SD)

GROUP II MALE SUBJECTS

Exposure Time: 3 Hr

Week	Day	No. of Subjects	Baseline	Immediate Exit	5 Min Post	15 Min Post	30 Min Post	1 Hr Post	2 Hr Post	3 Hr Post
				Chamber Concentration: 20 ppm (Steady)						
2	2	4	0	4.07 ±1.16	1.26 ±0.40	0.84 ±0.24	0.57 ±0.21	0.38 ±0.10	0.22 ±0.06	0.10 ±0.02
2	3	3	0.07 ±0.04	3.87 ±1.22	1.43 ±0.35	0.70 ±0.05	0.54 ±0.16	0.44 ±0.09	0.21	N.A.
2	4	3	Data unavailable for this day (N.A.)						0.17 ±0.06	0.11 ±0.06
2	5	4	0.03	1.69 ±0.43	0.78 ±0.17	0.64 ±0.21	0.40 ±0.12	0.25 ±0.03	0.11 ±0.00	0.11
				Chamber Concentration: 100 ppm (Steady)						
3	1	4	0.19 ±0.08	22.46 ±4.86	9.15 ±1.99	6.92 ±2.41	3.82 ±1.19	2.73 ±0.81	1.42 ±0.49	0.82 ±0.13
3	2	4	0.17 ±0.06	23.33 ±6.02	8.20 ±0.92	5.96 ±1.46	4.25 ±1.16	2.43 ±0.33	1.21	0.73 ±0.23
3	3	4	0.27 ±0.12	17.97 ±2.35	6.59 ±1.30	4.52 ±0.71	2.92 ±0.49	2.25 ±0.30	1.48 ±0.52	1.16 ±0.14
3	4	3	0.28 ±0.08	17.60 ±1.53	8.11 ±2.76	4.18 ±1.41	3.00 ±0.36	2.07 ±0.52	1.14 ±0.24	0.93 ±0.48
3	5	4	0.20 ±0.05	18.43 ±3.74	7.15 ±1.48	5.07 ±1.23	3.67 ±0.84	1.98 ±0.28	1.28 ±0.16	0.69 ±0.23
		21 hr post	0.21 ±0.04							

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TABLE V (continued)

TOLUENE CONCENTRATION IN ALVEOLAR BREATH, IN PPM (±SD)

GROUP II MALE SUBJECTS

Exposure Time: 3 Hr

eek	Day	No. of Subjects	Baseline	Immediate Exit	5 Min Post	15 Min Post	30 Min Post	1 Hr Post	2 Hr Post	3 Hr Post
				Chamber Concentration: 50 ppm						
4	1	3	0.11 ±0.00	8.18 ±1.82	4.02 ±1.13	2.47 ±0.68	1.23 ±0.10	1.07 ±0.27	0.72 ±0.29	0.30 ±0.06
4	2	4	0.11 ±0.00	9.87 ±2.28	2.88 ±1.03	2.23 ±0.45	1.52 ±0.32	1.09 ±0.16	0.37 ±0.10	0.24 ±0.06
4	3	4	0.14 ±0.06	13.13 ±3.47	5.83 ±1.74	3.57 ±0.86	2.18 ±0.79	1.43 ±0.51	0.95 ±0.35	0.37 ±0.15
4	4	4	0.22 ±0.05	No samples run -- "Zero" exposure						
				Chamber Concentration: 100 ppm (Fluctuating)						
5	1	4	0.09 ±0.00	20.98 ±2.78	5.37 ±0.40	4.73 ±1.48	3.03 ±0.47	2.25 ±0.85	0.99 ±0.18	0.50 ±0.21
5	2	3	0.20 ±0.05	17.52 ±4.79	6.81 ±0.94	4.63 ±1.57	2.99 ±0.54	1.83 ±0.21	1.54 ±0.15	0.51 ±0.24
5	3	4	0.19 ±0.03	No samples run - "Zero" exposure						

TABLE VI

TOLUENE CONCENTRATION IN ALVEOLAR BREATH, IN PPM (± SD)

GROUP III MALE SUBJECTS

Exposure Time: 1 Hr

Week	Day	No. of Subjects	Baseline	Immediate Exit	5 Min Post	15 Min Post	30 Min Post	1 Hr Post	2 Hr Post	3 Hr Post
			Chamber Concentration: 20 ppm (Steady)							
2	2	2	0	2.77 ±0.54	1.08 ±0.23	0.74 ±0.10	0.48 ±0.13	N.A.	0.13 ±0.00	0.11 ±0.03
2	3	2	0.04 ±0.00	3.72 ±0.33	1.50 ±0.00	0.91 ±0.06	0.77 ±0.00	0.43 ±0.06	N.A.	N.A.
2	4	2	Data unavailable for this day (N.A.)						0.11 ±0.06	0.08 ±0.02
2	5	2	0.04	1.81 ±0.40	0.71 ±0.08	0.56 ±0.08	0.43 ±0.11	0.25 ±0.06	N.A.	0.11
			Chamber Concentration: 100 ppm (Steady)							
3	1	2	0.14 ±0.00	21.48 ±2.92	5.84 ±1.35	4.99 ±0.45	3.71 ±0.00	2.14 ±0.72	0.64 ±0.13	0.27 ±0.04
3	2	2	0.12	19.72 ±2.86	6.26 ±0.27	4.43 ±0.36	3.41 ±0.54	2.40 ±0.00	0.89 ±0.11	0.53 ±0.18
3	3	2	0.20 ±0.06	16.07 ±2.65	6.04 ±1.15	3.92 ±0.69	3.26 ±0.00	2.29 ±0.23	1.11 ±0.23	0.51 ±0.27
3	4	2	0.16 ±0.04	16.99 ±1.07	6.64 ±0.55	4.86 ±0.56	3.63 ±0.87	2.24 ±0.47	0.77 ±0.12	0.36 ±0.16
3	5	2	0.06 ±0.03	27.09 ±2.19	10.45 ±2.30	7.51 ±2.52	5.27 ±1.97	3.33 ±0.98	0.53	0.22
		23 Hr Post	0.11 ±0.03							

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TABLE VI (Cont'd)

TOLUENE CONCENTRATION IN ALVEOLAR BREATH, IN PPM (± SD)

GROUP III MALE SUBJECTS

Exposure Time: 1 Hr

Week	Day	No. of Subjects	Baseline	Immediate Exit	5 Min Post	15 Min Post	30 Min Post	1 Hr Post	2 Hr Post	3 Hr Post
			Chamber Concentration: 50 ppm (Steady)							
4	1	2	0.05 ±0.00	9.48 ±0.62	4.32 ±0.74	2.86 ±0.33	1.90 ±0.12	1.31 ±0.04	0.40 ±0.08	0.29 ±0.08
4	2	2	0.05 ±0.03	10.16 ±0.65	3.73 ±0.11	3.33 ±0.67	1.37 ±0.00	1.20 ±0.24	0.28	0.09
4	3	2	0.05 ±0.03	8.49 ±0.13	3.45 ±0.27	2.29 ±0.06	1.63 ±0.20	1.08 ±0.06	0.50 ±0.14	0.25 ±0.07
4	4	2	0.09 ±0.00	no samples run - "zero" exposure						
			Chamber Concentration: 100 ppm (Fluctuating)							
5	1	2	0.05 ±0.03	10.98 ±2.52	4.14 ±0.65	2.59 ±0.57	2.07 ±0.49	1.61 ±0.16	0.64 ±0.10	0.32 ±0.03
5	2	2	0.08 ±0.04	12.97 ±3.97	5.42	4.44	3.45	2.66	0.60 ±0.01	0.55 ±0.08

TABLE VII

TOLUENE CONCENTRATION IN ALVEOLAR BREATH, IN PPM (± SD)

GROUP I FEMALE SUBJECTS

Exposure Time: 7-1/2 Hr

Week	Day	No. of Subjects	Baseline	Immediate Exit	5 Min Post	15 Min Post	30 Min Post	1 Hr Post	2 Hr Post	3 Hr Post
				Chamber Concentration: 100 ppm (Steady)						
2	1	4	0	19.50 ±3.25	8.37 ±0.77	6.05 ±0.41	5.18 ±0.56	3.46 ±0.19	1.52 ±0.29	0.96 ±0.24
2	2	4	0.23 ±0.04	16.22 ±4.08	7.02 ±0.71	5.06 ±0.64	3.90 ±0.53	3.44 ±0.43	1.80 ±0.35	1.52 ±0.30
2	3	4	0.48 ±0.06	23.68 ±5.35	11.88 ±1.58	6.93 ±0.88	4.96 ±0.73	4.17 ±0.27	1.68 ±0.86	0.89 ±0.53
2	4	4	0.49 ±0.04	16.91 ±3.91	8.38 ±1.50	5.53 ±1.56	4.18 ±1.08	3.18 ±0.40	2.11 ±0.60	1.14 ±0.33
2	5	4	0.54 ±0.11	27.45 ±7.26	12.59 ±2.52	8.75 ±1.68	5.09 ±2.33	5.76 ±0.09	3.53 ±0.58	2.65 ±0.48
		16 Hr Post	1.23 ±0.28							

TABLE VIII

TOLUENE CONCENTRATION IN ALVEOLAR BREATH, IN PPM (± SD)

GROUP II FEMALE SUBJECTS

Exposure Time: 3 Hr

Week	Day	No. of Subjects	Baseline	Immediate Exit	5 Min Post	15 Min Post	30 Min Post	1 Hr Post	2 Hr Post	3 Hr Post
			Chamber Concentration: 100 ppm (Steady)							
2	1	4	0	15.97 ±2.39	6.26 ±0.94	3.74 ±0.51	2.77 ±0.80	1.44 ±0.38	0.94 ±0.20	0.56 ±0.19
2	2	4	0.13 ±0.03	14.40 ±2.02	6.44 ±0.97	3.42 ±0.93	2.65 ±0.46	1.86 ±0.11	1.09 ±0.20	0.98 ±0.19
2	3	4	0.14 ±0.05	20.46 ±2.51	8.75 ±1.40	5.27 ±1.31	3.65 ±0.59	2.37 ±0.47	0.98 ±0.05	0.55 ±0.19
2	4	4	0.15 ±0.06	13.74 ±1.79	5.40 ±0.69	3.32 ±0.56	2.39 ±0.51	1.67 ±0.31	0.95 ±0.23	0.82 ±0.17
2	5	4	0.22 ±0.07	13.23 ±2.04	6.36 ±0.98	3.53 ±0.43	2.38 ±0.37	2.07 ±0.31	1.71 ±0.25	1.23 ±0.16
		21 Hr Post	0.51 ±0.21							

TABLE IX

TOLUENE CONCENTRATION IN ALVEOLAR BREATH, IN PPM (± SD)

GROUP III FEMALE SUBJECTS

Exposure Time: 1 Hr

Week	Day	No. of Subjects	Baseline	Immediate Exit	5 Min Post	15 Min Post	30 Min Post	1 Hr Post	2 Hr Post	3 Hr Post
				Chamber Concentration: 100 ppm						
2	1	2	0	10.54 ±1.15	4.14 ±0.35	2.52 ±0.34	1.94 ±0.00	0.81 ±0.00	0.46 ±0.06	0.36 ±0.00
2	2	2	0.10 ±0.04	10.79 ±0.48	3.88 ±0.69	1.94 ±0.69	1.50 ±0.62	1.07 ±0.13	0.38 ±0.13	0.37 ±0.12
2	3	2	0.10 ±0.02	15.53 ±0.37	4.28 ±0.84	2.30 ±0.83	1.45 ±0.37	0.99 ±0.09	0.42 ±0.11	0.22 ±0.00
2	4	2	0.09 ±0.03	8.97 ±0.87	2.37	1.71 ±0.40	1.23 ±0.27	0.95 ±0.00	0.51 ±0.04	0.29
2	5	2	0.06 ±0.00	9.66	3.82 ±0.77	2.10 ±0.00	1.68 ±0.39	1.13 ±0.17	0.99 ±0.14	0.67 ±0.07
		23 Hr Post	0.12 ±0.08							

TABLE X

TOLUENE CONCENTRATION IN BLOOD, IN PPM

GROUP I. MALE SUBJECTS

Exposure Time: 7-1/2 hr

Date	Subject No.	Pre-Exposure	Pre-Exit	15 Min Post
	Chamber Concentration: 20 ppm (Steady)			
3-12-74	169	0	<0.001	<0.001
Wk 2	203	0	<0.001	<0.001
Day 2	202	- Absent	-	-
	204	0	<0.001	<0.001
3-15-74	169	0	0.53	0.24
Wk 2	202	0	0.44	0.24
Day 5	203	0	0.27	0.19
	204	0	0.51	0.21
	Chamber Concentration: 100 ppm (Steady)			
3-18-74	169	0	3.65	1.80
Wk 3	203	0	3.65	1.50
Day 1				
3-22-74	169	0	3.00	1.75
Wk 3	203	0	2.65	1.20
Day 5				
	Chamber Concentration: 50 ppm (Steady)			
3-25-74	169	0	2.00	1.15
Wk 4	203	0	1.50	0.65
Day 1				

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TABLE X (Continued)

TOLUENE CONCENTRATION IN BLOOD, IN PPM

GROUP I. MALE SUBJECTS

Exposure Time: 7-1/2 hr

Date	Subject No.	Pre-Exposure	Pre-Exit	15 Min Post
	Chamber Concentration: 0 ppm			
3-29-74	169	0	0	0
Wk 4	203	0	0	0
Day 5				
	Chamber Concentration: 100 ppm (Fluctuating)			
4-1-74	169	0	3.65	2.40
Wk 5	203	0	3.30	1.85
Day 1				
	Chamber Concentration: 0 ppm			
4-5-74	169	0	Not run	not run
Wk 5	203	0	" "	" "

TABLE XI

TOLUENE CONCENTRATION IN BLOOD, IN PPM

GROUP II. MALE SUBJECTS

Exposure Time: 3 hr

Date	Subject No.	Pre-Exposure	Pre-Exit	15 Min Post
Chamber Concentration: 20 ppm (Steady)				
3-12-74	205	0	Since Group I manifested negligible amts., Group II, III not run at this concentration.	
Wk 2	206	0		
Day 2	207	0		
	208	0		
3-15-74	205	0	0.22	0.18
Wk 2	206	0	0.27	<0.001
Day 5	207	0	0.19	<0.005
	208	0	0.29	0.19
Chamber Concentration: 100 ppm (Steady)				
3-18-74	205	0	4.15	1.20
Wk 3	206	0	4.50	0.95
Day 1	207	0	6.00	2.75
	208	0	3.75	1.35
3-22-74	205	0	3.45	1.75
Wk 3	206	0	3.00	1.90
Day 1	207	0	3.15	2.30
	208	0	3.10	1.20
Chamber Concentration: 50 ppm (Steady)				
3-25-74	205	- Absent	-	-
Wk 4	206	0	1.60	0.50
Day 1	207	0	1.55	1.00
	208	0	1.58	0.70

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TABLE XI (Continued)

TOLUENE CONCENTRATION IN BLOOD, IN PPM

GROUP II. MALE SUBJECTS

Exposure Time: 3 hr

Date	Subject No.	Pre-Exposure	Pre-Exit	15 Min Post
	Chamber Concentration: 0 ppm			
3-29-74	205	0	0	0
Wk 4	206	0	0	0
Day 5	207	0	0	0
	208	0	0	0
	Chamber Concentration: 50, 100, 150 (Fluctuating) TWA - 100 ppm			
4-1-74	205	0	3.55	2.45
Wk 5	206	0	3.45	2.10
Day 1	206	0	3.85	2.55
	208	0	3.55	2.75
	Chamber Concentration: 0 ppm			
4-5-74	205	0	0	not run
Wk 5	206	0	0	" "
Day 5	207	0	0	" "
	208	0	0	" "

TABLE XII

TOLUENE CONCENTRATION IN BLOOD, IN PPM

GROUP III. MALE SUBJECTS

Exposure Time: 1 hr

Date	Subject No.	Pre-Exposure	Pre-Exit	15 Min Post
	Chamber Concentration: 20 ppm (Steady)			
3-12-74 Wk 2 Day 2	209	0	Since Group I manifested negligible amts., Group II, III not run at this concentration.	
3-15-74	209	0	<0.001	<0.001
Wk 2	210	0	<0.001	<0.001
Day 5				
	Chamber Concentration: 100 ppm (Steady)			
3-18-74	209	0	3.75	0.60
Wk 3	210	0	2.90	0.75
Day 1				
3-22-74	209	0	2.55	no sample
Wk 3	210	0	2.80	1.55
Day 5				
	Chamber Concentration: 50 ppm (Steady)			
3-25-74	209	0	2.00	0.35
Wk 4	210	0	2.00	0.35
Day 1				
	Chamber Concentration: 0			
3-29-74	209	0	0	0
Wk 4	210	0	0	0
Day 5				

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TABLE XII (Continued)

TOLUENE CONCENTRATION IN BLOOD, IN PPM

GROUP III. MALE SUBJECTS

Exposure Time: 1 hr

Date	Subject No.	Pre-Exposure	Pre-Exit	15 Min Post
	Chamber Concentration: 50, 100, 150 ppm (Fluctuating) TWA - 100 ppm			
4-1-74	209	0	2.80	1.65
Wk 5	66	0	2.45	2.00
Day 1				
	Chamber Concentration: 0			
4-5-74	209	0	0	not run
Wk 5	66	0	0	" "
Day 5				

TABLE XIII

TOLUENE CONCENTRATION IN BLOOD, IN PPM

FEMALE SUBJECTS

Chamber Concentration: 100 ppm (Steady)

Date	Subject No.	Pre-exposure	Pre-exit	15 Min Post
		Group I Exposure Time: 7-1/2 Hr		
4/22/74	178	0	3.05	1.90
Wk 2	211	0	3.40	1.84
Day 1	212	0	3.00	2.10
	213	0	3.90	2.70
4/26/74	178	0	2.80	1.54
Wk 2	211	0	3.65	2.32
Day 5	212	0	4.15	1.85
	213	0	2.95	1.85
		Group II Exposure Time: 3 Hr		
4/22/74	95	0	2.75	1.54
Wk 2	214	0	3.05	2.32
Day 1	215	0	2.60	1.85
	216	0	2.85	1.85
4/26/74	95	0	2.85	1.22
Wk 2	214	0	3.00	1.55
Day 5	215	0	3.30	1.45
	216	0	2.65	1.00
		Group III Exposure Time: 1 Hr		
4/22/74	217	0	2.80	1.20
Wk 2 Day 1	218	0	2.20	1.30
4/26/74	217	0	2.20	0.45
Wk 2 Day 5	218	0	1.85	0.95

TABLE XIV

EXCRETION OF HIPPURIC ACID BY HUMANS EXPOSED TO TOLUENE VAPOR

Toluene Exposure Conc.	MALES 0 ppm	MALES 20 ppm	MALES 50 ppm	MALES 100 ppm	FEMALES 0 ppm	FEMALES 100 ppm
	Group I - 7-1/2 hr				Group I - 7-1/2 hr	
No. of Samples*	12	12	6	14	7	20
Mean, g/24 hr	1.60	1.63	2.17	2.89	1.70	2.87
± SD	0.67	0.73	0.33	0.88	1.12	1.03
Range	0.78-2.88	0.73-3.27	1.80-2.64	1.88-4.86	0.67-3.69	1.21-4.90
	Group II - 3 hr				Group II - 3 hr	
No. of Samples*	18	13	11	24	6	20
Mean, g/24 hr	0.82	1.42	1.26	1.77	2.00	2.77
± SD	0.27	0.78	0.72	0.64	0.50	0.90
Range	0.50-1.52	0.68-2.86	0.57-2.72	0.67-3.33	1.32-2.56	1.52-4.35
	Group III - 1 hr				Group III - 1 hr	
No. of Samples*	8	8	6	11	4	10
Mean, g/24 hr	1.45	2.05	3.24	2.87	1.23	1.32
± SD	1.10	0.98	1.17	1.30	0.50	0.63
Range	0.34-3.13	0.91-3.79	1.56-4.88	1.07-4.84	0.79-1.83	0.73-2.51

* Represents the total number of corrected 24-hr urine values used to obtain the mean, SD, and range.

TABLE XV

F AND PAIRED t VALUES FOR COMPARISON OF PRE-EXPOSURE TO TOLUENE EXPOSURE VER WAVE AMPLITUDES

Exposure Conc. ppm	Subject 169 Wave 3 D.F. 2/2		Subject 203 W3		W4 D.F. 2/2		W5	
	F	t	F	t	F	t	F	t
20	5.583	1.956	3.013	1.496	+41.700	.636	2.798	2.891*
20	6.171	.386	17.442	1.292	19.148	.456	1.523	1.145
100	7.444	.434	7.496	.499	+61.470	.203	2.314	1.231
100	1.652	.397	2.740	1.279	13.905	.311	604.000	1.012
100	7.444	3.165*	6.170	.062	+23.837	.545	5.388	1.305
50	2.255	.576	1.628	.020	3.209	.051	7.367	1.136
50	67.000	1.329	15.912	.451	+55.619	.319	1.648	.789
0	2.586	0	2.724	1.477	3.696	.467	1.449	.505
100Fluc.	1.281	1.284	3.384	.204	3.880	.417	+304.600	1.188
150	18.760	3.284*	5.367	1.494	5.615	.108	7.521	2.126
0	1.134	.316	8.806	.189	+20.490	.314	+27.969	.724
0	1.392	.352	1.909	.699	4.846	.107	1.498	1.345

+Significant at P=.05

*Significant at P=.01

TABLE XVI

PARAMETERS USED TO EVALUATE THE FUNCTIONAL INTEGRITY OF PULMONARY AIRWAYS DURING EXPOSURE TO TOLUENE

Wk	Day	Toluene Conc. ppm	FVC l-BTPS	FEV_1/FVC %	PEFR l/sec	MMEF l/sec
			Group I (Individual values)			
1	4	0	6.00	78.30	9.80	5.00
			5.47	80.00	12.10	4.90
2	4	20	5.65	81.80	10.40	5.60
			4.78	84.10	10.90	4.82
3	4	100	5.60	83.10	10.40	5.10
			5.10	84.90	13.10	5.10
4	4	0	4.80		8.40	4.50
			5.10		11.80	5.10
5	4	0	5.80	81.00	10.60	5.40
			4.95	84.00	12.70	5.00
			Group II (Means $\pm$ SEM)			
1	4	0	5.99	85.60	13.00	6.60
			0.41	0.74	0.87	0.60
5	4	0	6.13	85.20	12.90	7.00
			0.40	2.30	1.00	0.40

FVC = Maximum volume in ℓ of air exhaled after a maximum inspiration.
FEV_1/FVC = Per cent of FVC exhaled in one sec.
PEFR = Maximum rate of air flow during FVC maneuver.
MMEF = Maximum rate of air flow at mid-point of FVC.

TABLE XVII

PARAMETERS USED TO EVALUATE THE REGULATION

OF VENTILATION, HEART RATE, AND ALVEOLAR GAS EXCHANGE

DURING EXPOSURE TO TOLUENE

Resting Subjects

Wk	Day	Toluene Conc. ppm	$\dot{V}_E/\dot{V}O_2$ 1-BTPS / 1-STPD	$PaCO_2$ mm Hg	pHa	$P_{A_{O_2}}$ mm Hg	$D_L CO$ ml/min / mm Hg	H.R. Beats/min.
			Mean Values (±SEM), 4 Subjects					
1	4	0	35.6 ±0.8	39.7 ±1.0	7.382 ±0.017	103.70 ±1.02	31.3 ±1.6	83.5 ±9.5
2	4	20	35.9 ±0.4	43.5 ±0.7	7.393 ±0.006	101.4 ±1.2	30.2 ±2.3	74.8 ±3.5
			Mean Values, 2 Subjects					
1	4	0	38.4	40.2	7.385	104.5	30.2	95.0
2	4	20	37.7	43.2	7.395	101.2	31.0	80.0
3	4	100	37.9	41.5	7.398	102.2	--	95.0
4	4	0	40.4	42.9	7.373	102.8	32.3	97.5
5	4	0	35.8	41.0	7.410	96.3	31.0	99.5

$D_L CO$ = Reflects capability of CO to move from lungs to blood.

$\dot{V}_E/\dot{V}O_2$ = Liters of air exhaled from lungs each min per liter utilization of oxygen.

Pa_{CO_2} = Partial pressure of CO_2 in arterial blood.

pHa = Reflects the acid-base status of arterial blood.

H.R. = Number of heart beats per min.

TABLE XVIII

PARAMETERS USED TO EVALUATE THE REGULATION

OF VENTILATION, HEART RATE, AND ALVEOLAR GAS EXCHANGE

DURING EXPOSURE TO TOLUENE

Exercising Subjects, 350 KPM - 6 Min

Wk	Day	Toluene Conc. ppm	$\dot{V}_E/\dot{V}O_2$ 1-BTPS / 1-STPD	$PaCO_2$ mm Hg	pHa	$P_{A_{O_2}}$ mm Hg	$D_L CO$ ml/min mm Hg	H.R. Beats/min.
			Mean Values (±SEM), 4 Subjects					
1	4	0	34.5 ±1.5	37.2 ±1.2	7.361 ±0.017	112.3 ±1.3	33.7 ±3.0	99.7 ±7.1
2	4	20	33.5 ±1.5	40.2 ±1.5	7.376 ±0.004	110.9 ±1.6	37.2 ±3.8	103.9 ±5.5
			Mean Values, 2 Subjects					
1	4	0	32.1	39.0	7.330	110.6	36.9	103.0
2	4	20	33.8	42.1	7.379	112.0	--	111.0
3	4	100	32.7	39.9	7.404	107.9	--	137.0
4	4	0	34.4	39.0	7.418	107.0	39.4	117.0
5	4	0	30.2	38.7	7.392	101.1	37.3	119.0

See Table XVII for definitions of parameters.

TABLE XIX

PARAMETERS USED TO EVALUATE THE REGULATION
OF VENTILATION, HEART RATE, AND ALVEOLAR GAS EXCHANGE
DURING EXPOSURE TO TOLUENE

Exercising Subjects, 750 KPM - 5 Min

Wk	Day	Toluene Conc. ppm	$\frac{\dot{V}_E}{\dot{V}O_2}$ $\frac{1\text{-BTPS}}{1\text{-STPD}}$	$PaCO_2$ mm Hg	pHa	$P_{A_{O_2}}$ mm Hg	$D_L CO$ $\frac{ml/min}{mm\ Hg}$	H.R. Beats/min.
			Mean Values (±SEM), 4 Subjects					
1	4	0	36.0 ±1.0	36.3 ±0.8	7.373 ±0.026	114.2 ±0.9	42.0 ±3.5	133.0 ±2.8
2	4	20	36.2 ±0.8	38.3 ±1.0	7.373 ±0.004	114.5 ±0.2	41.2 ±1.2	145.0 ±7.4
			Mean Values, 2 Subjects					
2	4	20	36.65	38.1	7.373	115.0	40.7	153.0
3	4	100	39.91	38.3	7.389	113.2	--	164.0
4	4	0	36.78	38.1	7.382	111.0	43.4	150.0
5	4	0	34.88	38.8	7.391	112.3	46.1	155.0

See Table XVII for definitions of parameters.

TABLE XX

PAIRED t VALUES FOR COMPARISON OF CONTROL VERSUS

EXPOSURE TEST SCORES

Exposure Time: 7-1/2 Hr

		Toluene Concentration							
		20 ppm		50 ppm		100 ppm		100 ppm fluctuating	
Test		t	df	t	df	t	df	t	df
Marquette Test:									
Sound Stimulus	E/S	-0.793	1	0.333	1	1.615	1	-1.390	1
	|E-S|	-0.065	1	2.390	1	0.858	1	-0.480	1
	RχT	0.019	1	2.545	1	-1.111	1	-0.651	1
Light Stimulus	E/S	-0.123	1	-0.721	1	-0.767	1	-0.200	1
	|E-S|	-0.095	1	0.622	1	-0.350	1	0.973	1
	RχT	0.296	1	0.419	1	0.824	1	-0.923	1
10 Sec Estimation		6.295	1	-0.616	1	1.609	1	-1.945	1
30 Sec Estimation		9.899*	1	-1.414	1	0.847	1	-0.670	1
Arithmetic Test		0.968	1	3.500	1	2.061	1	0.615	1
Coordination Test		2.000	1	2.800	1	4.155	1	-0.968	1
Inspection Test		0.714	1	-1.000	1	0.857	1	0.786	1

*Significant P $<.05$

**Significant P $<.01$

E/S = Estimate/Stimulus: E-S = Estimate-Stimulus: RχT = Reaction Time

TABLE XXI

PAIRED t VALUES FOR COMPARISON OF CONTROL VERSUS

EXPOSURE TEST SCORES

Exposure Time: 3 Hr

	Toluene Concentration							
	20 ppm		50 ppm		100 ppm		100 ppm fluctuating	
Test	t	df	t	df	t	df	t	df
Marquette Test:								
Sound Stimulus E/S	1.919	3	0.273	3	1.908	3	-0.058	3
Sound Stimulus |E-S|	0.993	3	2.207	3	2.403	3	1.868	3
Sound Stimulus RχT	0	3	-0.659	3	-1.796	3	-0.235	3
Light Stimulus E/S	-1.512	3	0.157	3	-0.946	3	-2.127	3
Light Stimulus |E-S|	2.709*	3	1.664	3	-0.463	3	0.996	3
Light Stimulus RχT	-1.568	3	-0.200	3	-0.859	3	-0.216	3
10 Sec Estimation	-0.927	3	0.369	3	1.334	3	-0.777	3
30 Sec Estimation	-0.397	3	0.991	3	1.032	3	2.317	3
Arithmetic Test	5.047**	3	-0.930	3	1.437	3	-1.308	3
Coordination Test	0.451	3	1.512	3	3.347*	3	0.573	3
Inspection Test	0.875	3	-1.255	3	0.017	3	-1.927	3

* Significant P $<.05$

** Significant P $<.01$

E/S = Estimate/Stimulus: |E-S| = Estimate-Stimulus: RχT = Reaction Time

TABLE XXII

ALERTNESS TEST

PAIRED-T TEST FOR MALE SUBJECTS

EXPOSED TO TOLUENE

GROUP I - 7 1/2 Hr Subj.

	Tuesday 3/12/74 20 ppm		Thursday 3/14/74 20 ppm		Tuesday 3/26/74 50 ppm		Tuesday 3/19/74 100 ppm		Thursday 3/21/74 100 ppm		Tuesday 4/2/74 100 ppm Fluct.	
	t	df	t	df	t	df	t	df	t	df	t	df
% Correct	0	1	.375	1	-2.141	1	.29	1	.73	1	0	1
Rx Time, Visual	1.131	1	N.A.		-5.681	1	-.459	1	.387	1	N.A.	
Rx Time Sound	-1.317	1	N.A.		-1.294	1	2.481	1	-7.667*	1	N.A.	

GROUP II - 3 Hr Subj.

% Correct	1.39	3	-1.511	2	.255	3	-.453	3	1.37	3	-.434	2
Rx Time, Visual	-.768	3	.619	1	.655	2	3.273*	2	1.27	2	N.A.	
Rx Time Sound	-.981	3	3.075*	1	-.41	2	2.522	2	1.609	2	N.A.	

*Significant at .05

Neg. value means an increase from control

TABLE XXIII

ALERTNESS TEST

PAIRED-T TEST FOR FEMALE SUBJECTS

EXPOSED TO TOLUENE

GROUP I - 7 1/2 Hr Subj.:

	Monday 4/22/74 100 ppm		Wednesday 4/24/74 100 ppm		Friday 4/26/74 100 ppm		Monday 4/29/74 0 ppm	
	t	df	t	df	t	df	t	df
% Correct	11.012	1	4.581*	2	5.544*	2	1.344	2
Rx Time, Visual	4.857*	2	.546	3	-.451	3	.599	3
Rx Time, Sound	1.694	2	.673	3	.189	3	1.032	3

GROUP II - 3 Hr Subj.:

% Correct	-3.150	3	-1.033	3	-2.342	3	-.467	3
Rx Time, Visual	1.792	3	.892	3	1.804	3	1.487	3
Rx Time, Sound	1.393	3	1.584	3	1.376	3	1.811	3

*Significant at .05

Neg. value means an increase from control

TABLE XXIV

SUMMARY OF SUBJECTIVE RESPONSES

DURING EXPOSURES TO TOLUENE

	0 ppm M & F	20 ppm M only	50 ppm M only	100 ppm M & F
Group I - 7-1/2 Hr				
No. of subject-days	24	15	6	34
Headaches	4	4	0	6
ENT irritations	3	0	0	2
Other	3	2	0	0
Group II - 3 Hr				
No. of subject-days	24	11	10	43
Headaches	7	3	4	11
ENT irritations	4	0	2	21
Other	3	0	0	2
Group III - 1 Hr				
No. of subject-days	15	7	6	24
Headaches	1	1	1	0
ENT irritations	0	1	0	3
Other	1	2	1	3

TABLE XXV

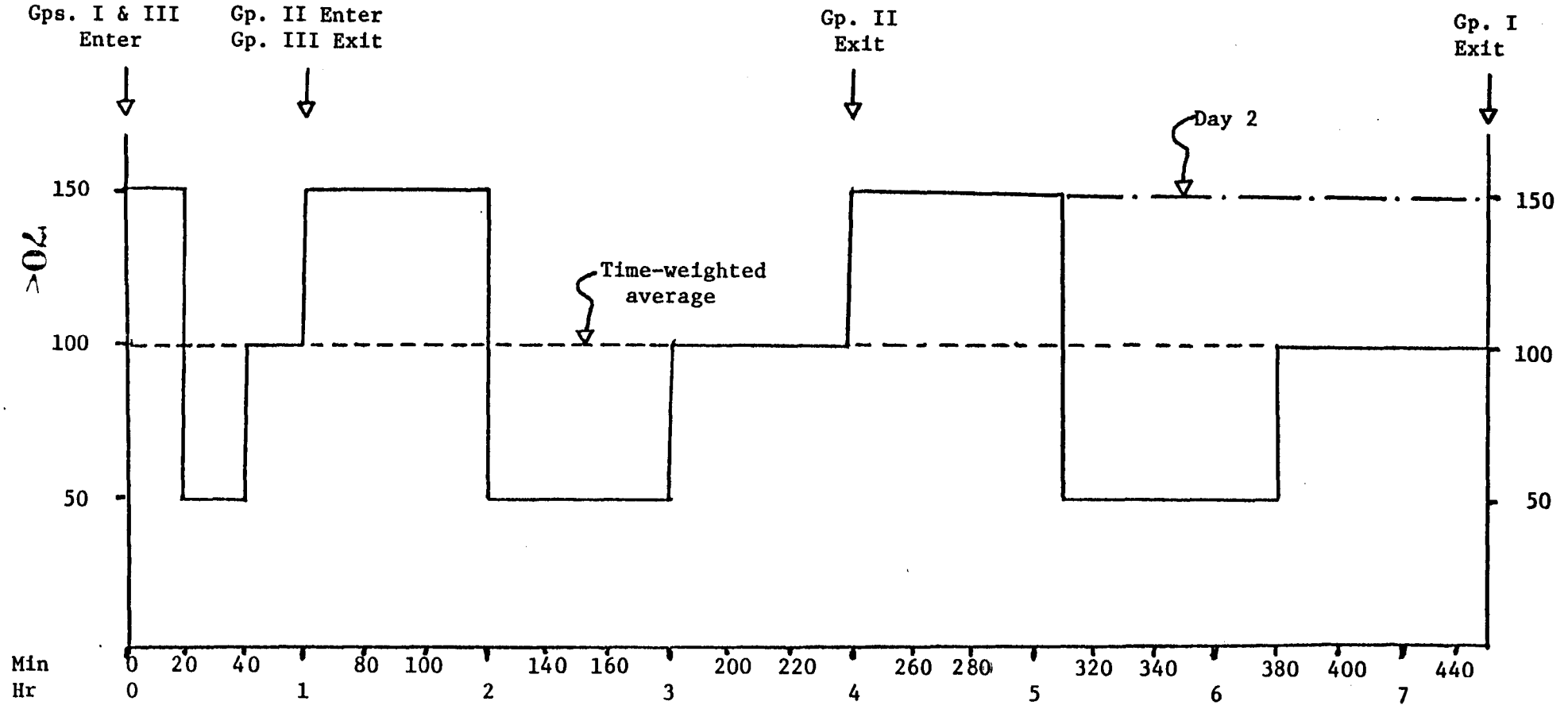
TOLUENE STABILITY IN BREATH CONTAINERS

	No. of Hr Post-Filling														
	0-Hr			24-Hr			72-Hr			120-Hr					
	Saran Bag	Glass Tube	Plastic Bottle	Saran Bag	Glass Tube	Plastic Bottle	Saran Bag	Glass Tube	Plastic Bottle	Saran Bag	Saran Bag Mailed	Glass Tube	Glass Tube Mailed	Plastic Bottle
o. Filled	4	10	4	4	11	2	4	5	2	4	1	5	5	1
o. Valid	4	7	2	3	10	2	3	5	2	2	1	4	5	1
ean Conc. n ppm	52.6	46.6	51.5	46.8	42.1	44.0	44.9	45.1	35.3	41.6	13.6	42.8	36.6	44.9
±SD	4.9	4.0	2.9	5.2	4.6	13.1	5.6	5.8	9.1	8.6		6.9	5.5	
SEM	2.4	1.5	2.0	3.0	1.5	9.3	3.2	2.6	6.4	6.0		3.4	2.5	
high	56.0	51.9	53.4	50.9	50.0	53.2	51.3	52.9	41.7	46.0		51.4	41.1	
low	45.4	40.4	49.5	41.0	36.6	34.7	41.5	40.1	28.9	37.2		36.0	30.4	
of Saran Bag t OHr	100	89	98	89	80	84	86	86	67	79	26	81	70	85

FIGURE 1

FLUCTUATION OF TOLUENE VAPOR CONCENTRATION IN CHAMBER

MALES, WEEK 5, DAYS 1 & 2



SPONTANEOUS EEG
MALE TOLUENE EXPOSURE

SUBJECT #169

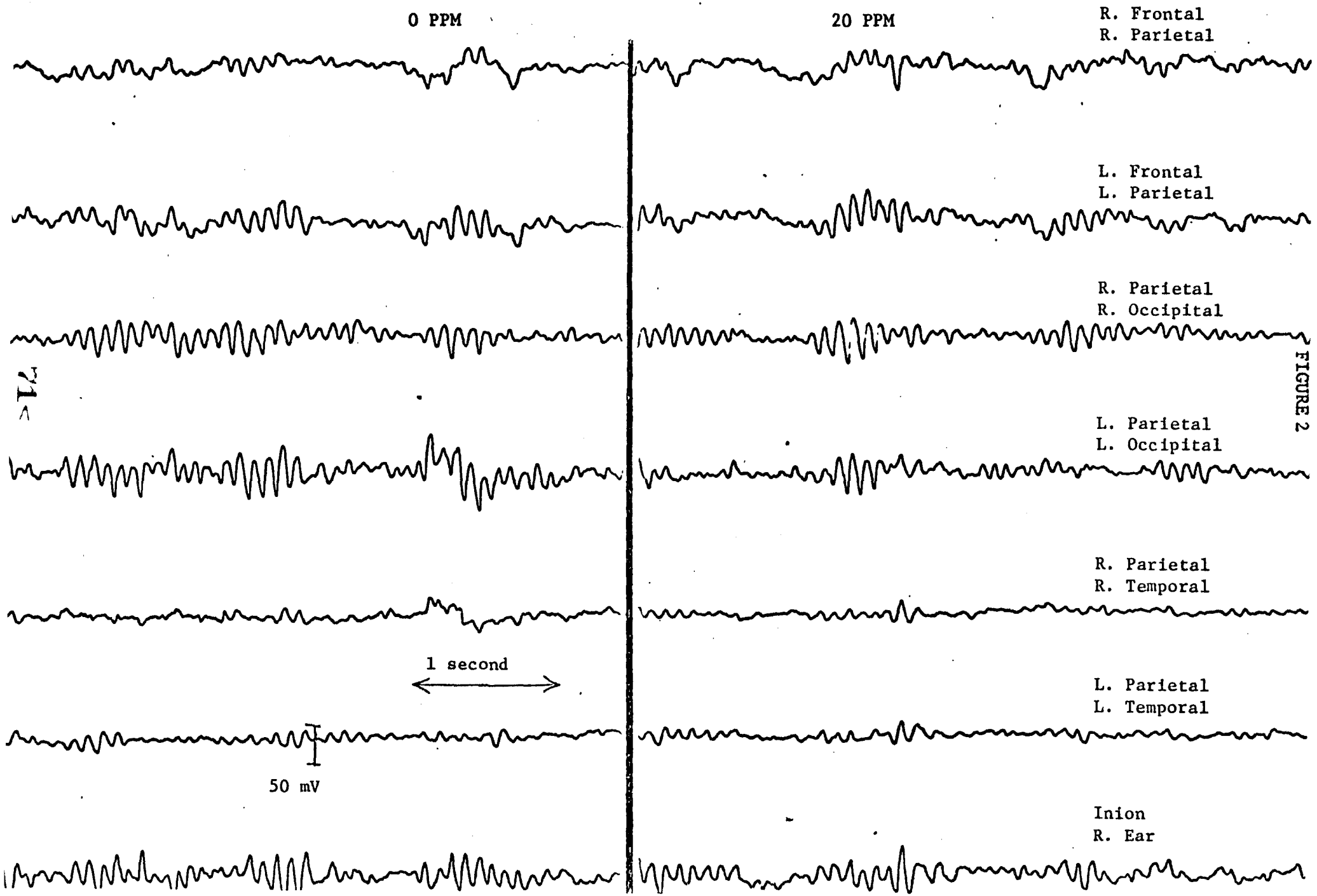
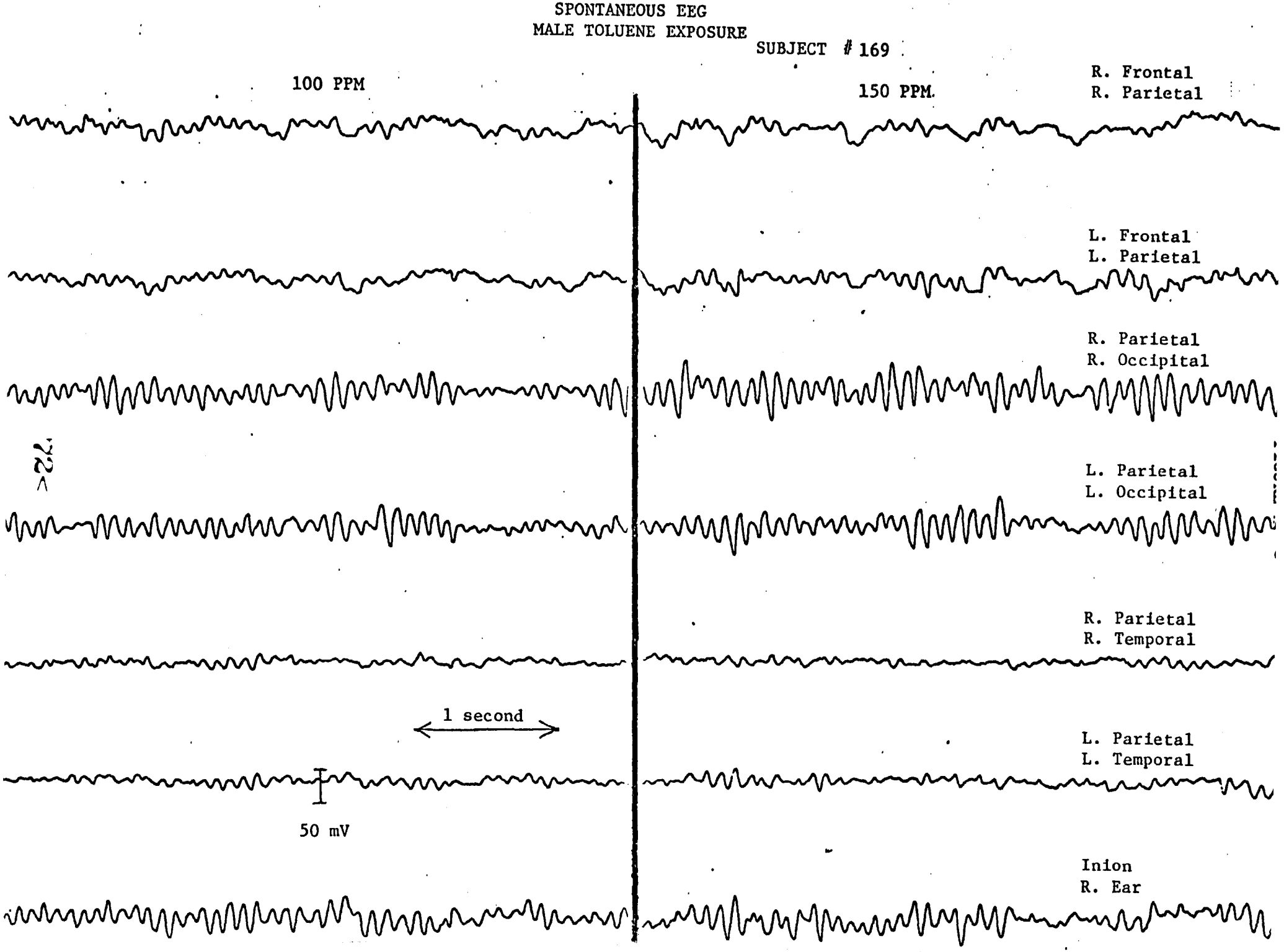


FIGURE 2


SPONTANEOUS EEG
MALE TOLUENE EXPOSURE
SUBJECT # 169
100 PPM
150 PPM.
R. Frontal
R. Parietal
L. Frontal
L. Parietal
R. Parietal
R. Occipital
L. Parietal
L. Occipital
R. Parietal
R. Temporal
L. Parietal
L. Temporal
Inion
R. Ear
1 second
50 mV

SPONTANEOUS EEG
MALE TOLUENE EXPOSURE

SUBJECT #178

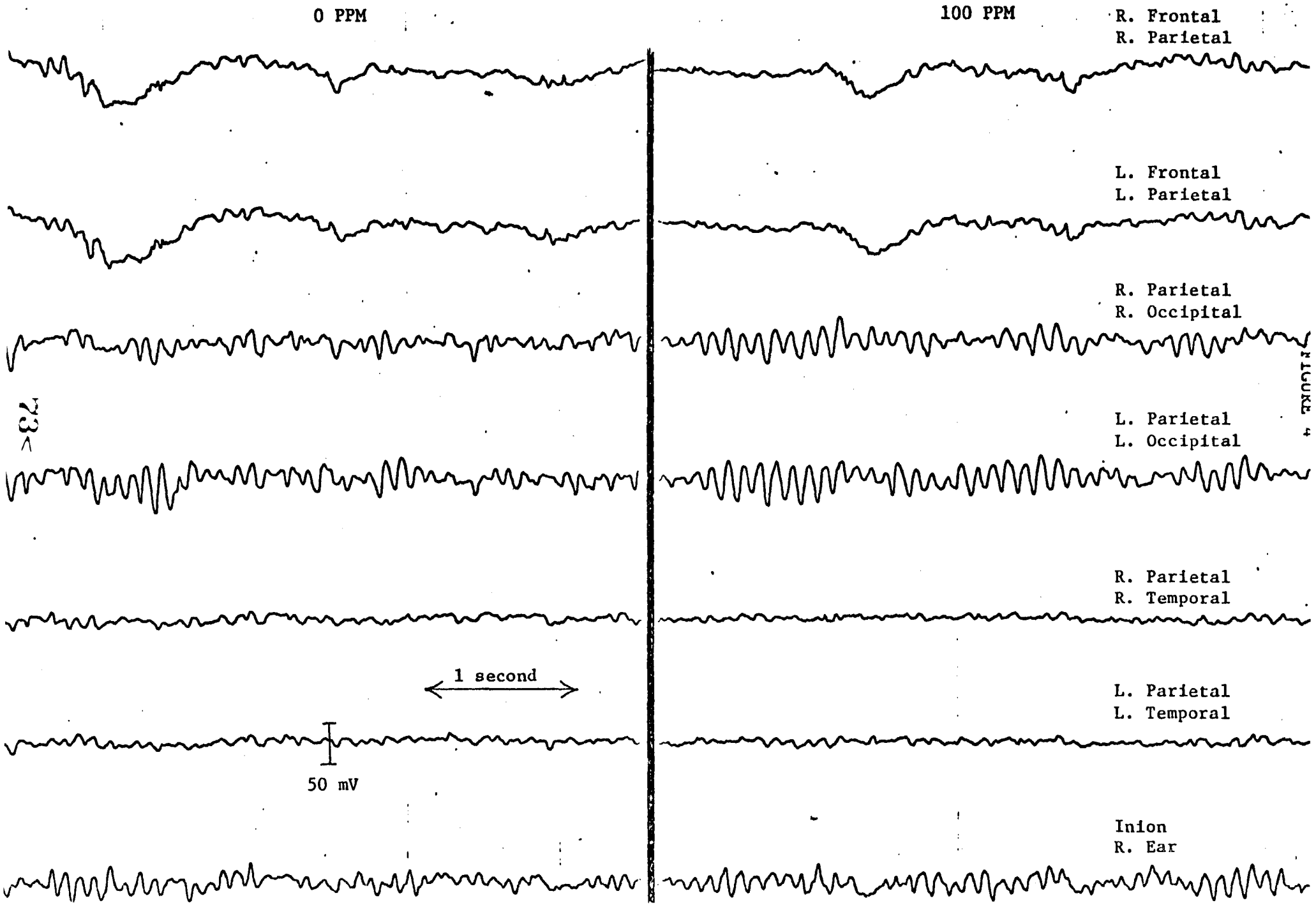


FIGURE 4

FIGURE 5

TOLUENE MALE VER'S

SUBJECT #169

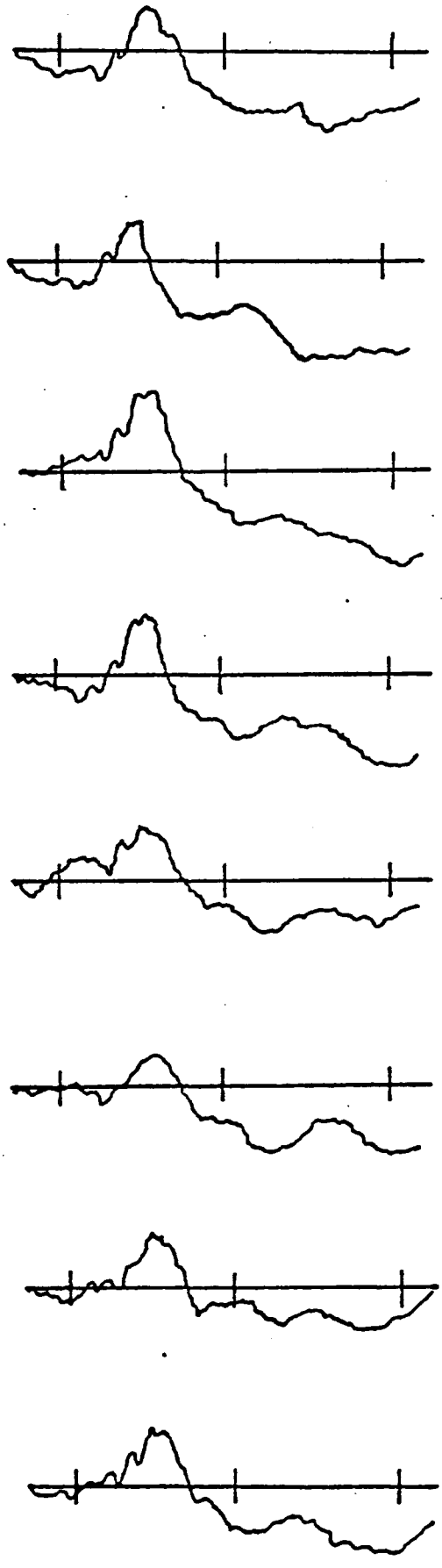
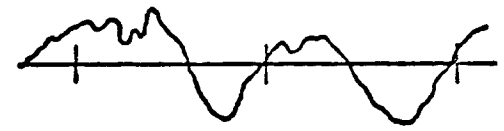


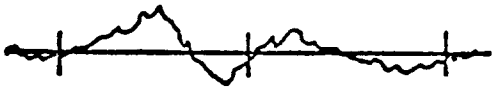
FIGURE 6

TOLUENE MALE VER'S

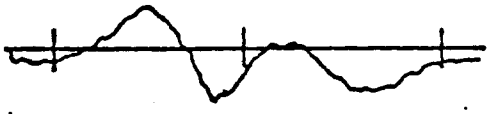
SUBJECT #203



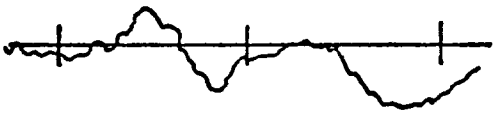
0 ppm



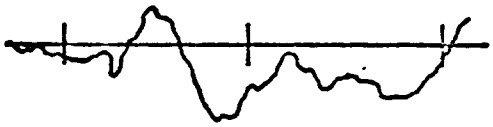
20 ppm



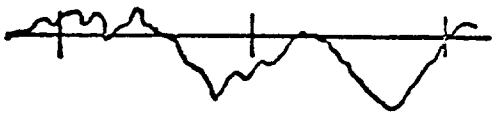
100 ppm



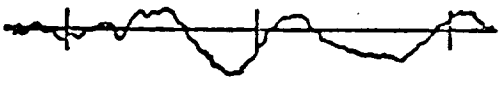
50 ppm



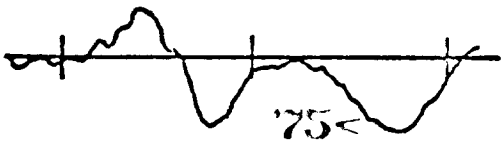
0 ppm



100 ppm
fluctuating



150 ppm

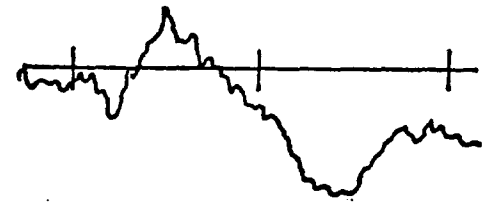


0 ppm

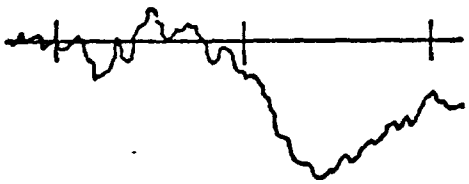
FIGURE 7

TOLUENE FEMALE VER'S

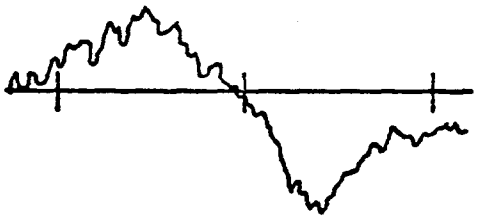
SUBJECT #178



0 ppm



100 ppm



100 ppm

100 ppm

0 ppm

FIGURE 8

EFFECT OF TRAINING AND EXPOSURE TO TOLUENE

ON TIME ESTIMATIONS - $7\frac{1}{2}$ HOUR SUBJECTS

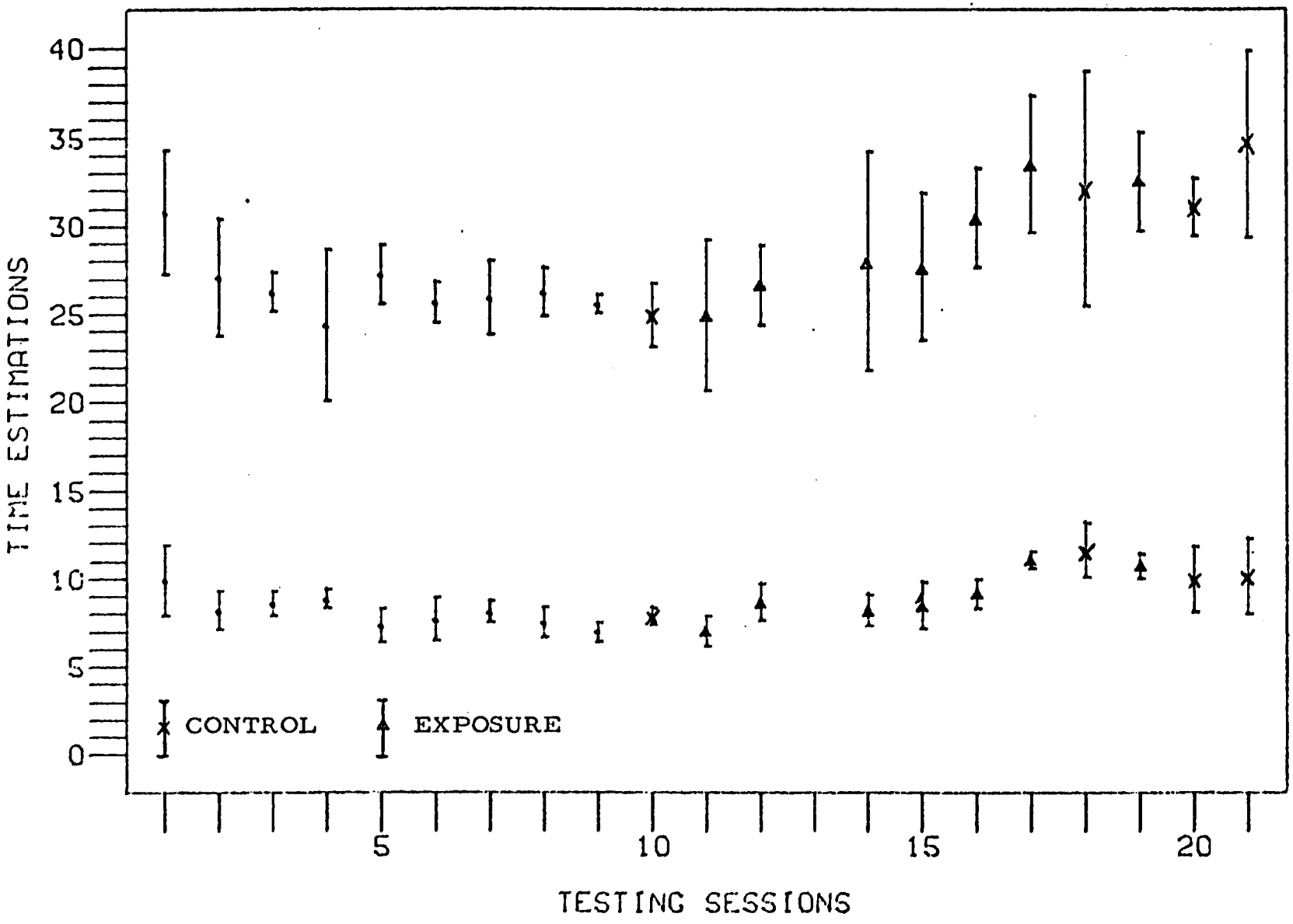


FIGURE 9

EFFECT OF TRAINING AND EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - $7\frac{1}{2}$ HOUR SUBJECTS

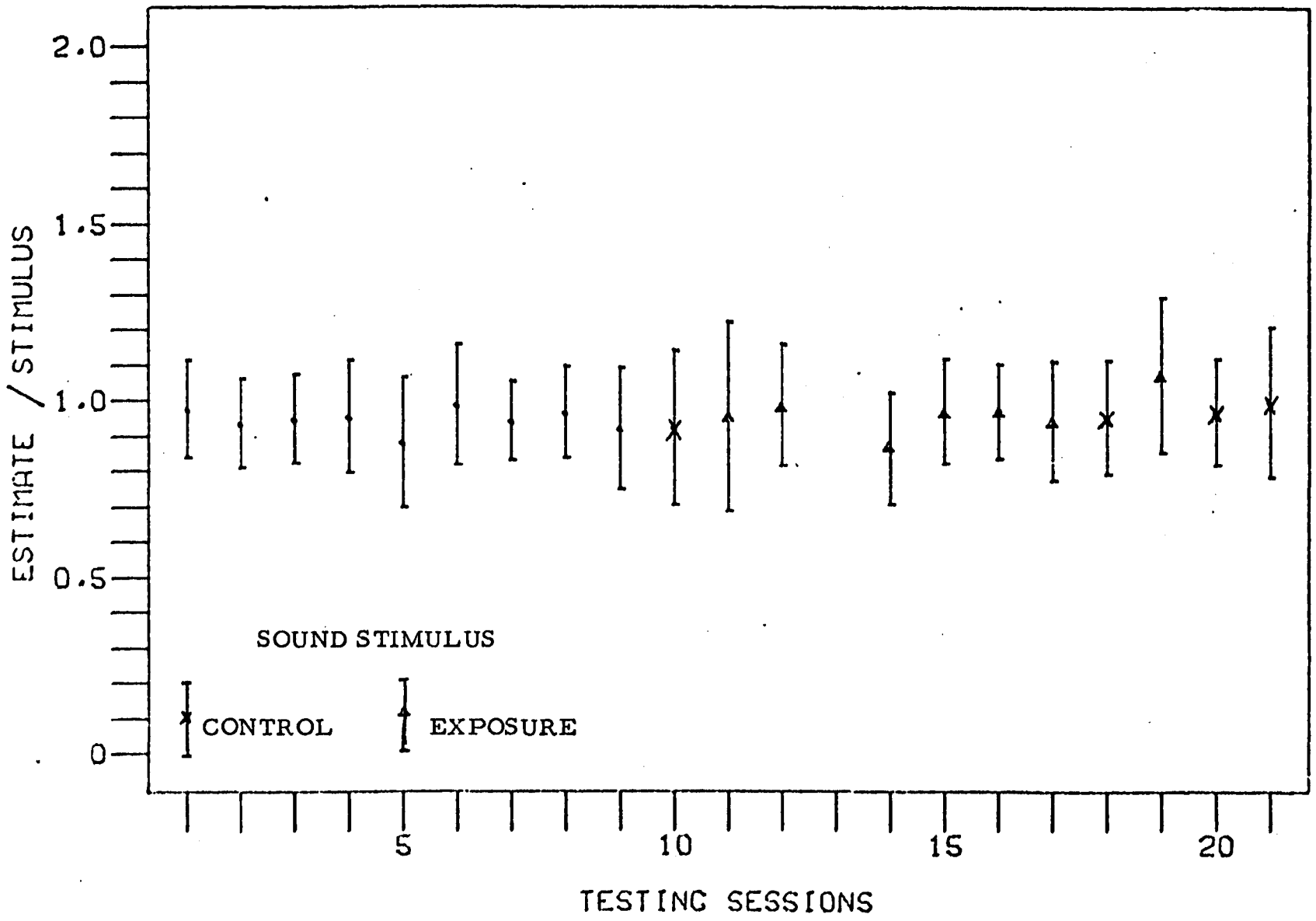


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FIGURE 10

EFFECT OF TRAINING AND EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - $7\frac{1}{2}$ HOUR SUBJECTS

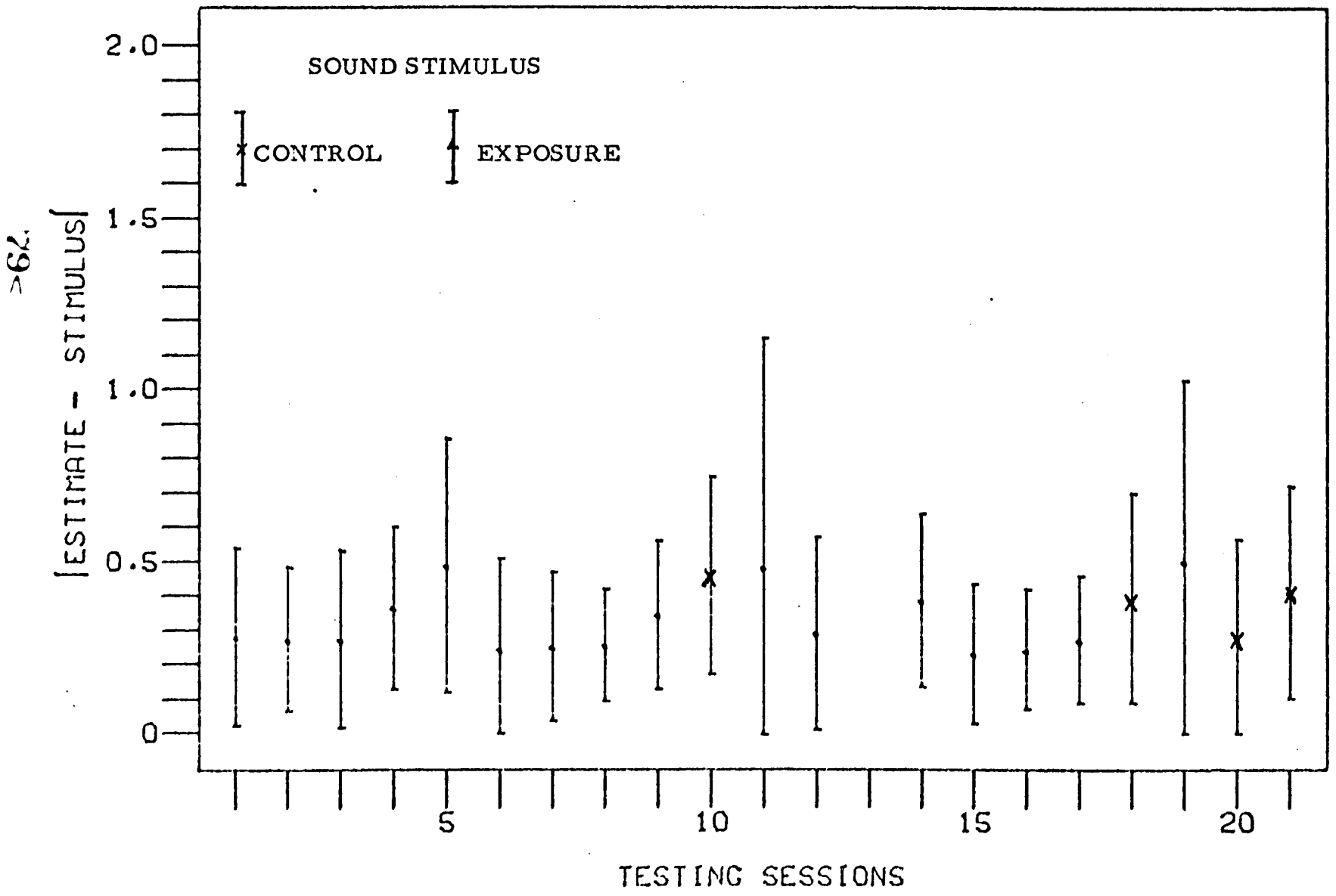

FIGURE 11

EFFECT OF TRAINING AND EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - $7\frac{1}{2}$ HOUR SUBJECTS

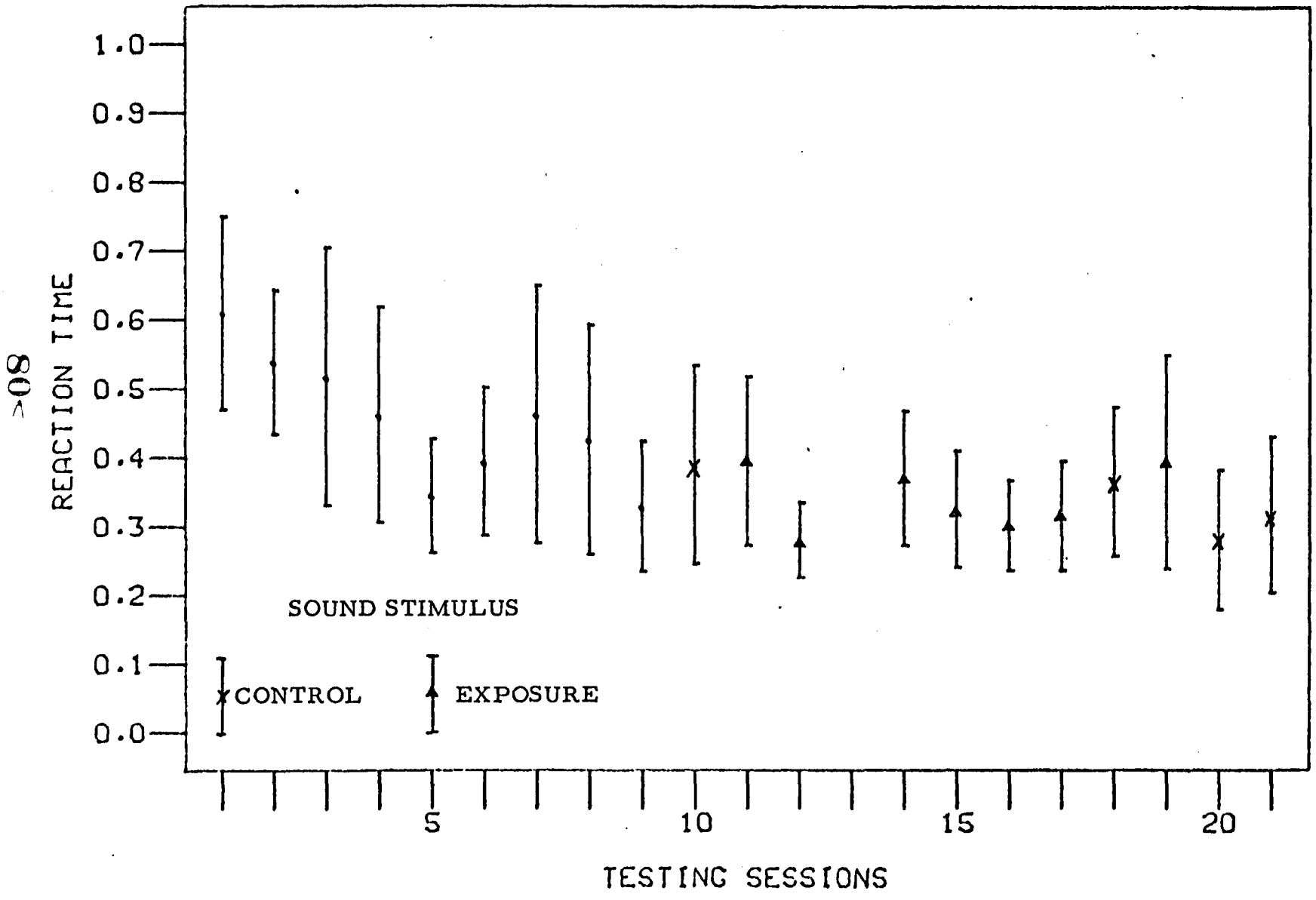

FIGURE 12

EFFECT OF TRAINING AND EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - $7\frac{1}{2}$ HOUR SUBJECTS

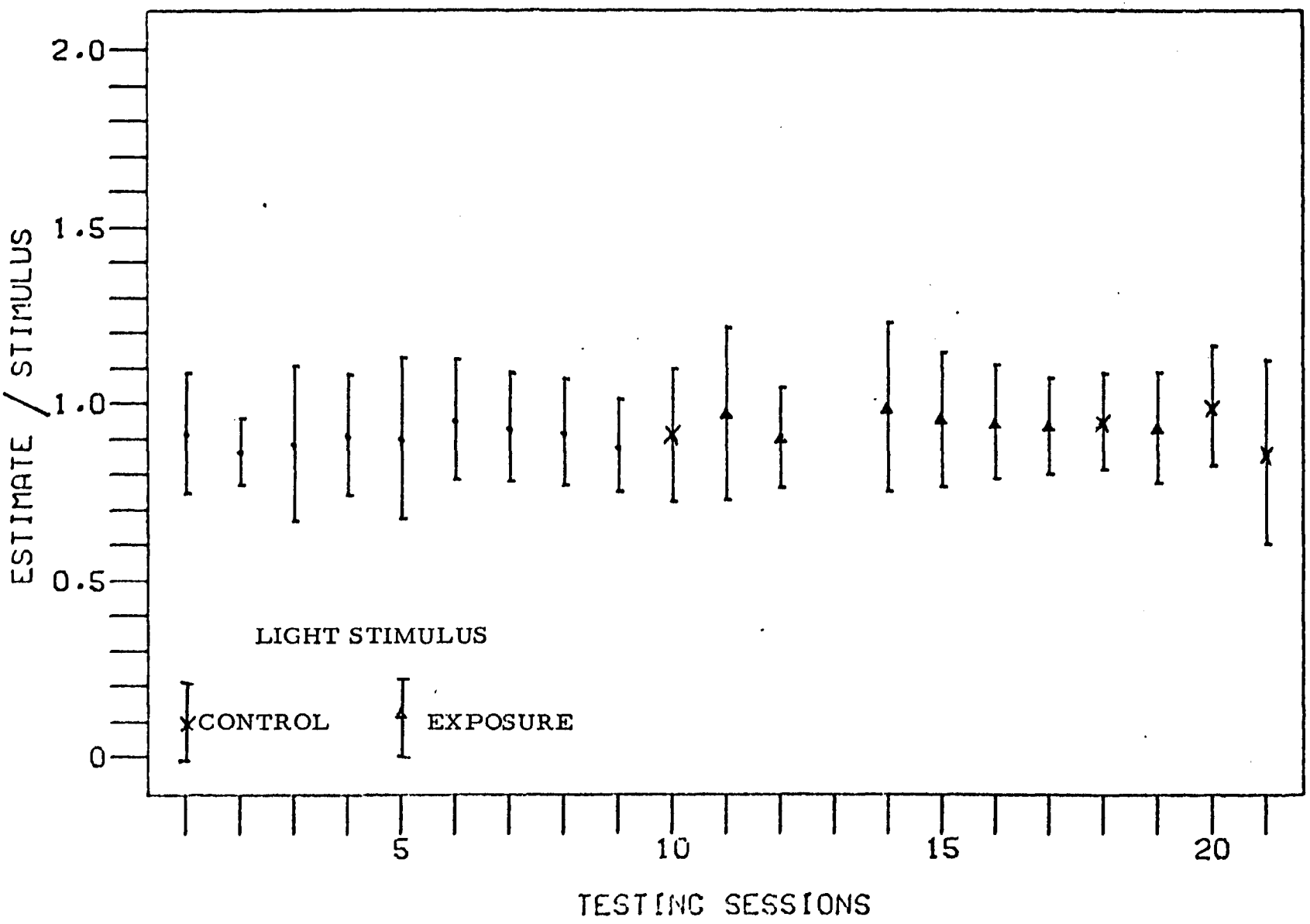

FIGURE 13

EFFECT OF TRAINING AND EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - $7\frac{1}{2}$ HOUR SUBJECTS

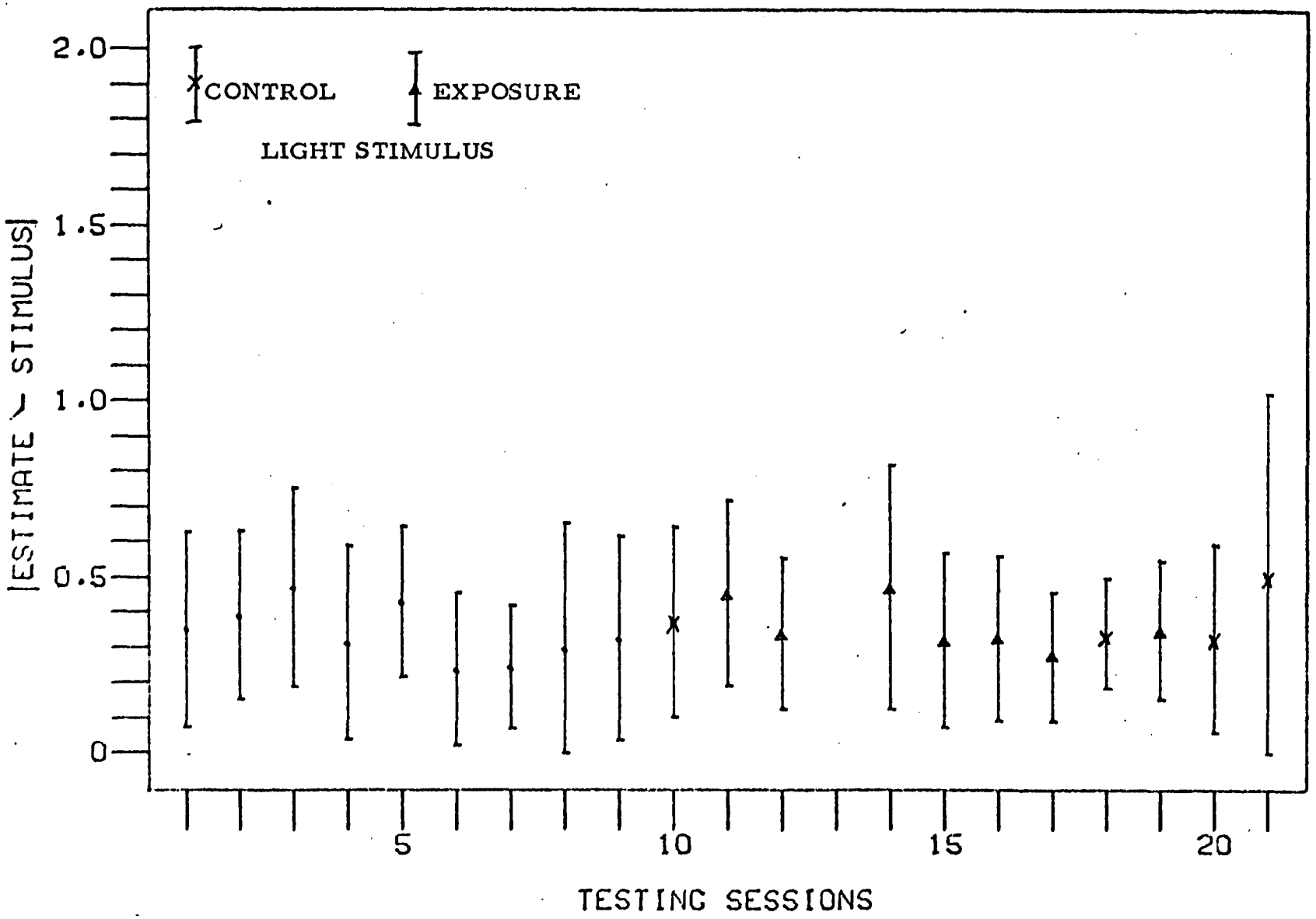

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FIGURE 14

EFFECT OF TRAINING AND EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - $7\frac{1}{2}$ HOUR SUBJECTS

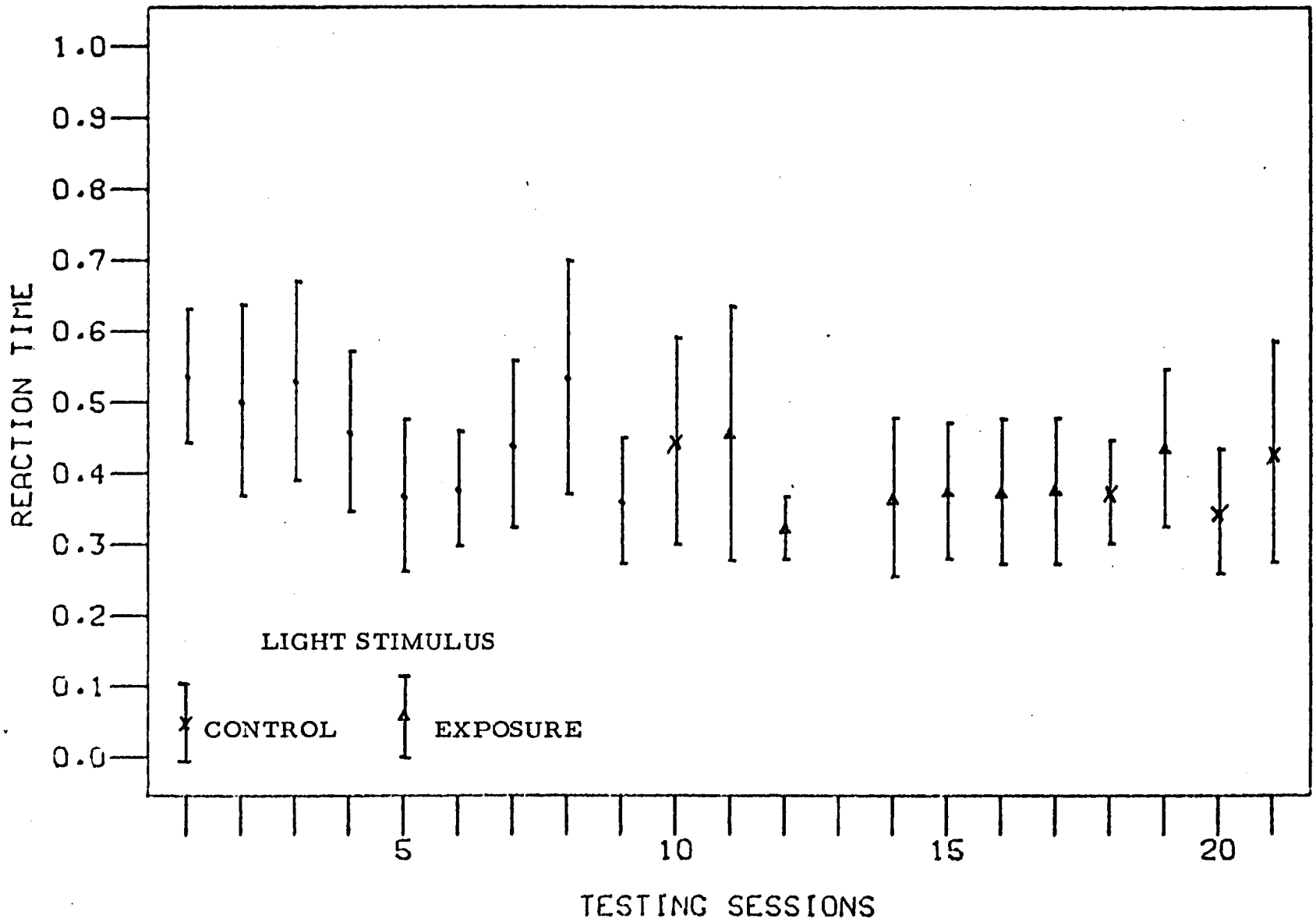


FIGURE 15

EFFECT OF TRAINING AND EXPOSURE TO TOLUENE

ON THE ARITHMETIC TEST - 7 1/2 HOUR SUBJECTS

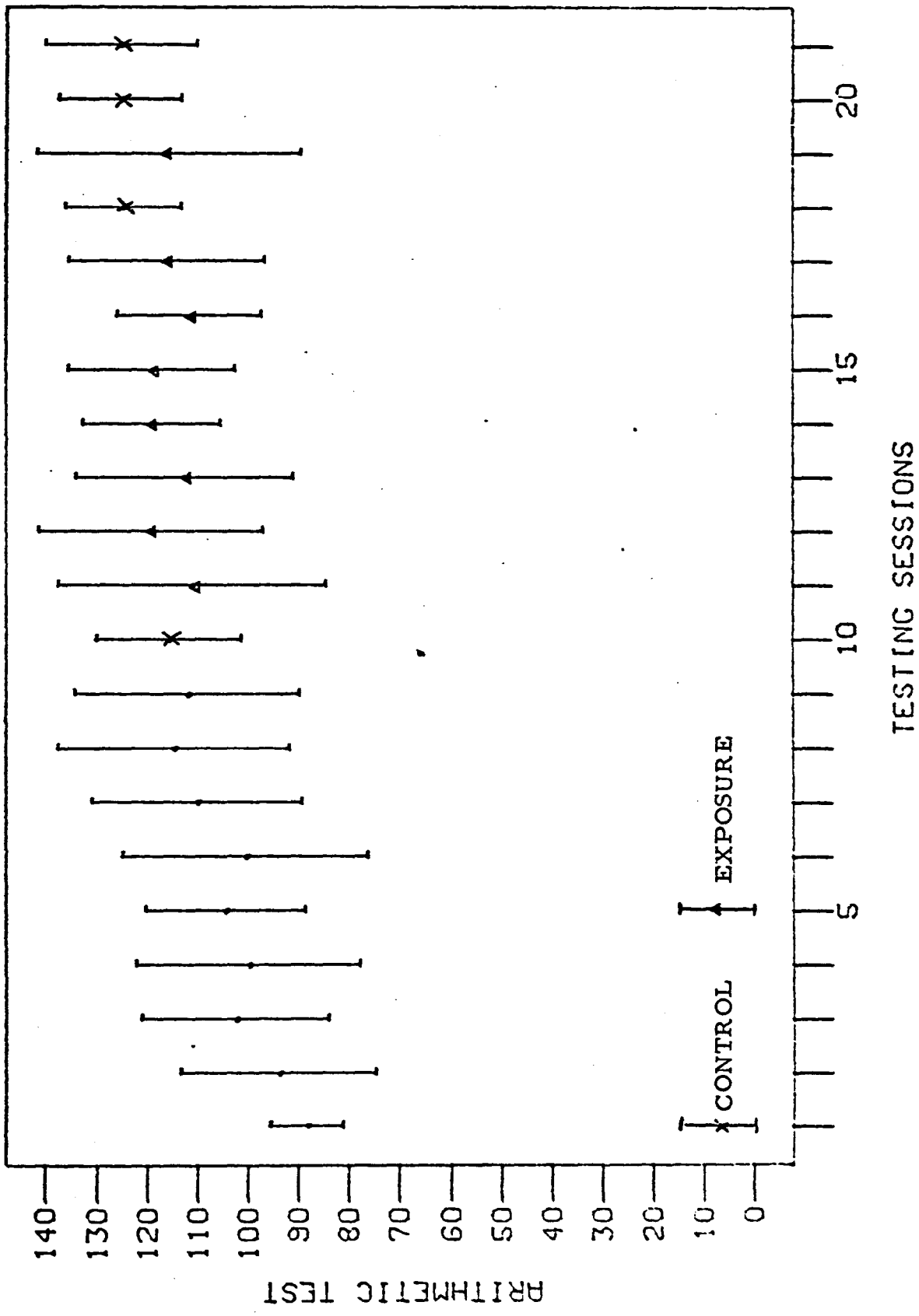


FIGURE 16

EFFECT OF TRAINING AND EXPOSURE TO TOLUENE

ON THE COORDINATION TEST - 7 1/2 HOUR SUBJECTS

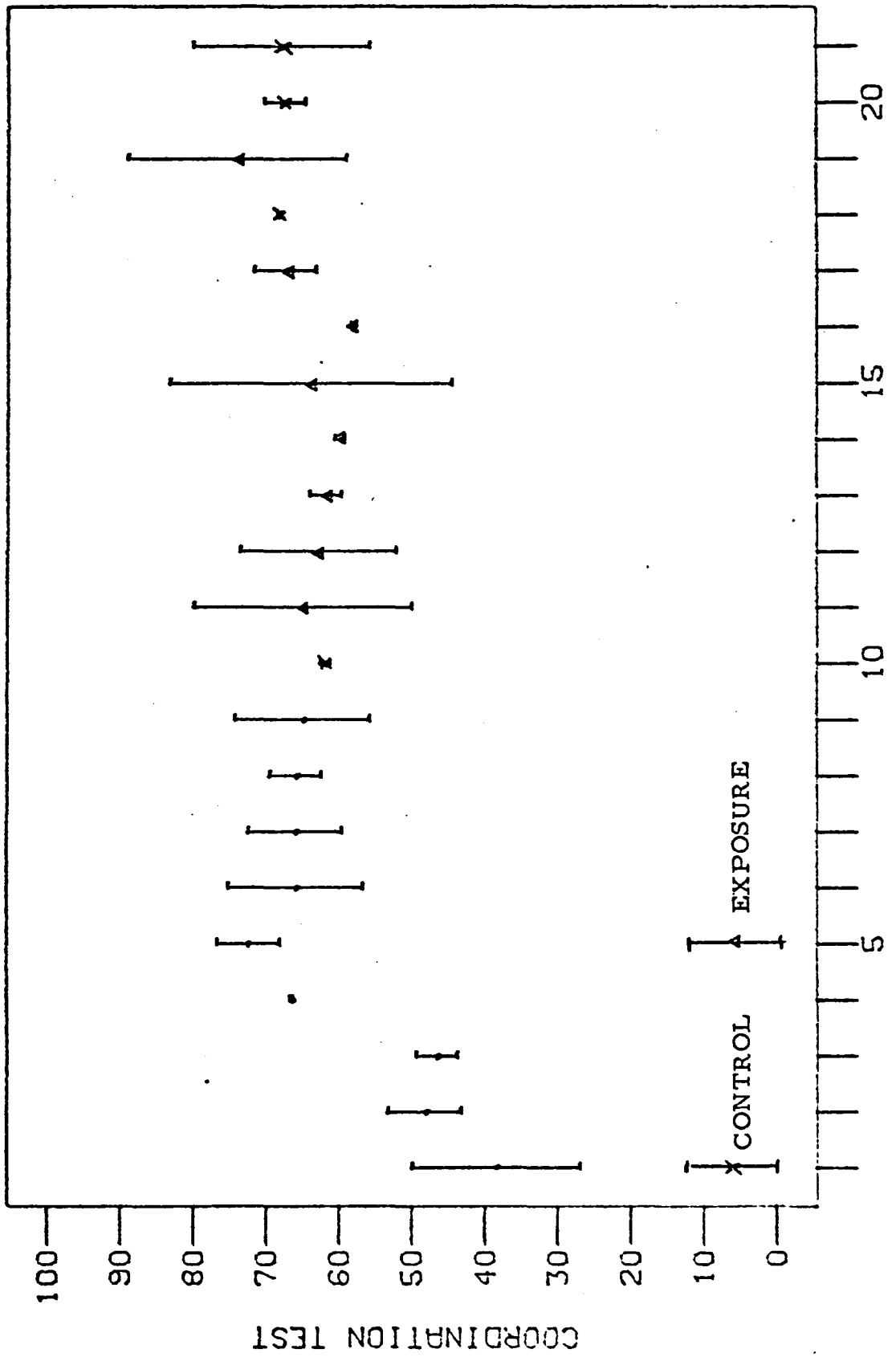


FIGURE 17

EFFECT OF TRAINING AND EXPOSURE TO TOLUENE

ON THE INSPECTION TEST - 7 1/2 HOUR SUBJECTS

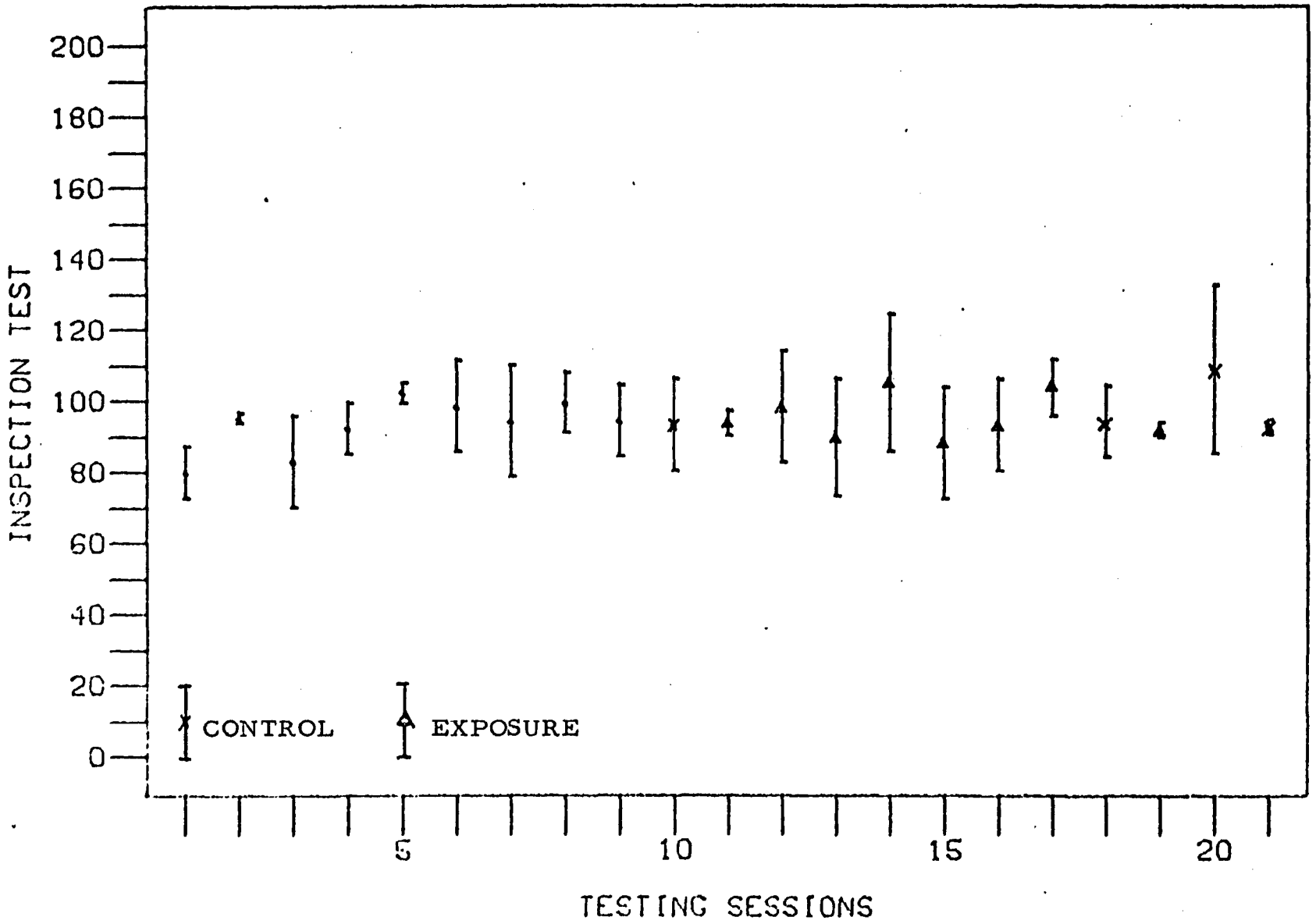


FIGURE 18

EFFECT OF TRAINING AND EXPOSURE TO TOLUENE

ON TIME ESTIMATIONS - 3 HOUR SUBJECTS

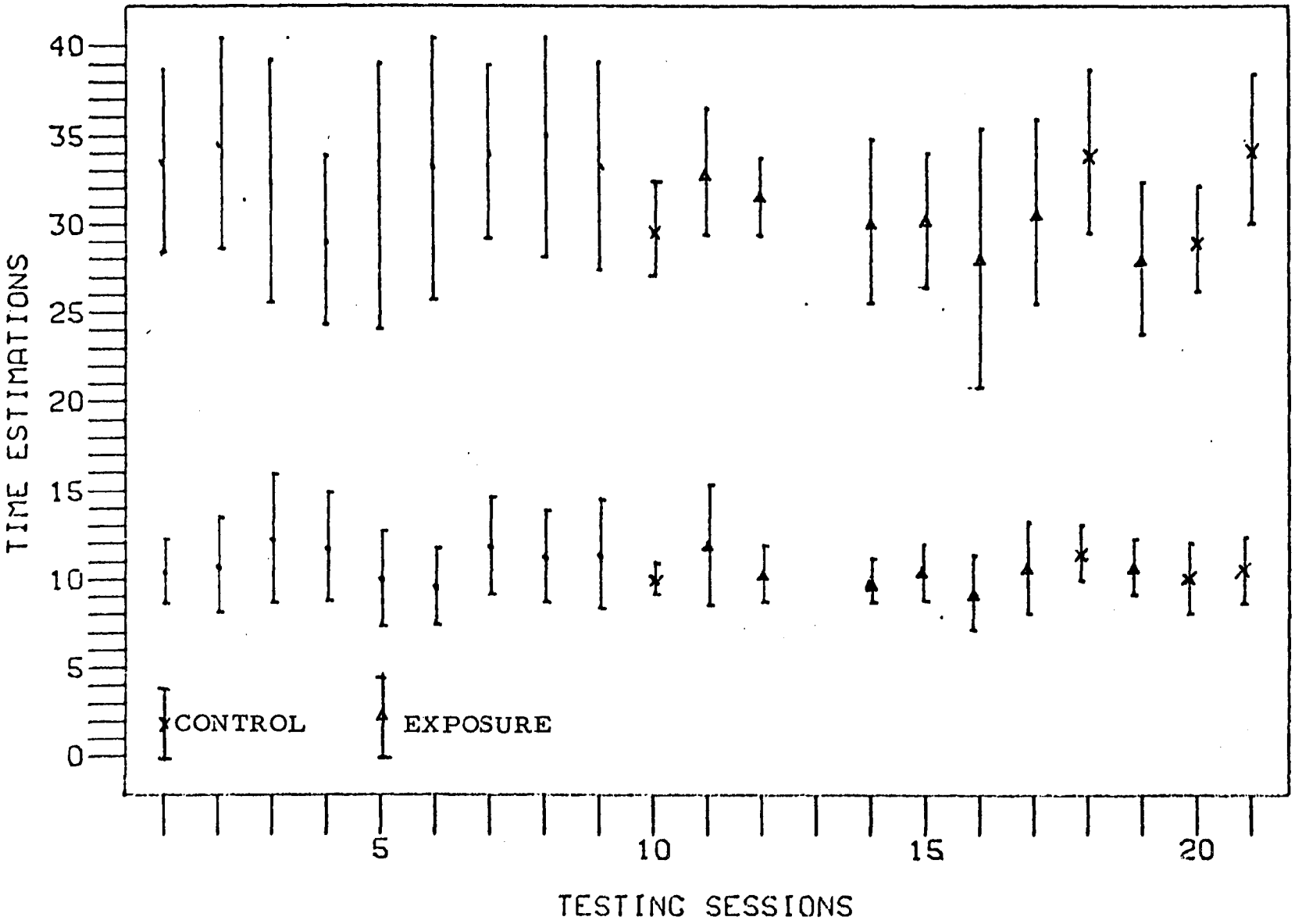


FIGURE 19

EFFECT OF TRAINING AND EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - 3 HOUR SUBJECTS

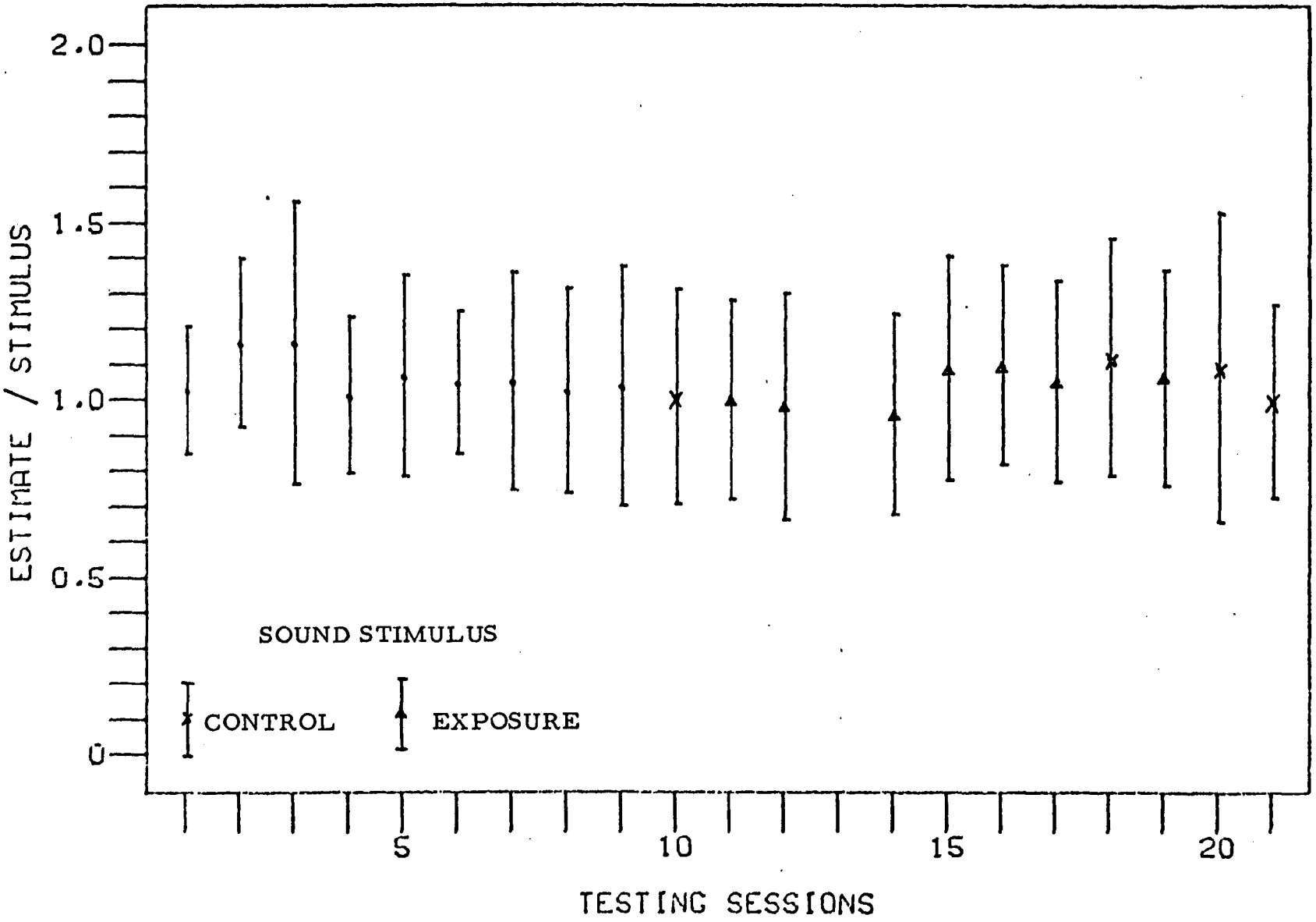


FIGURE 20

EFFECT OF TRAINING AND EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - 3 HOUR SUBJECTS

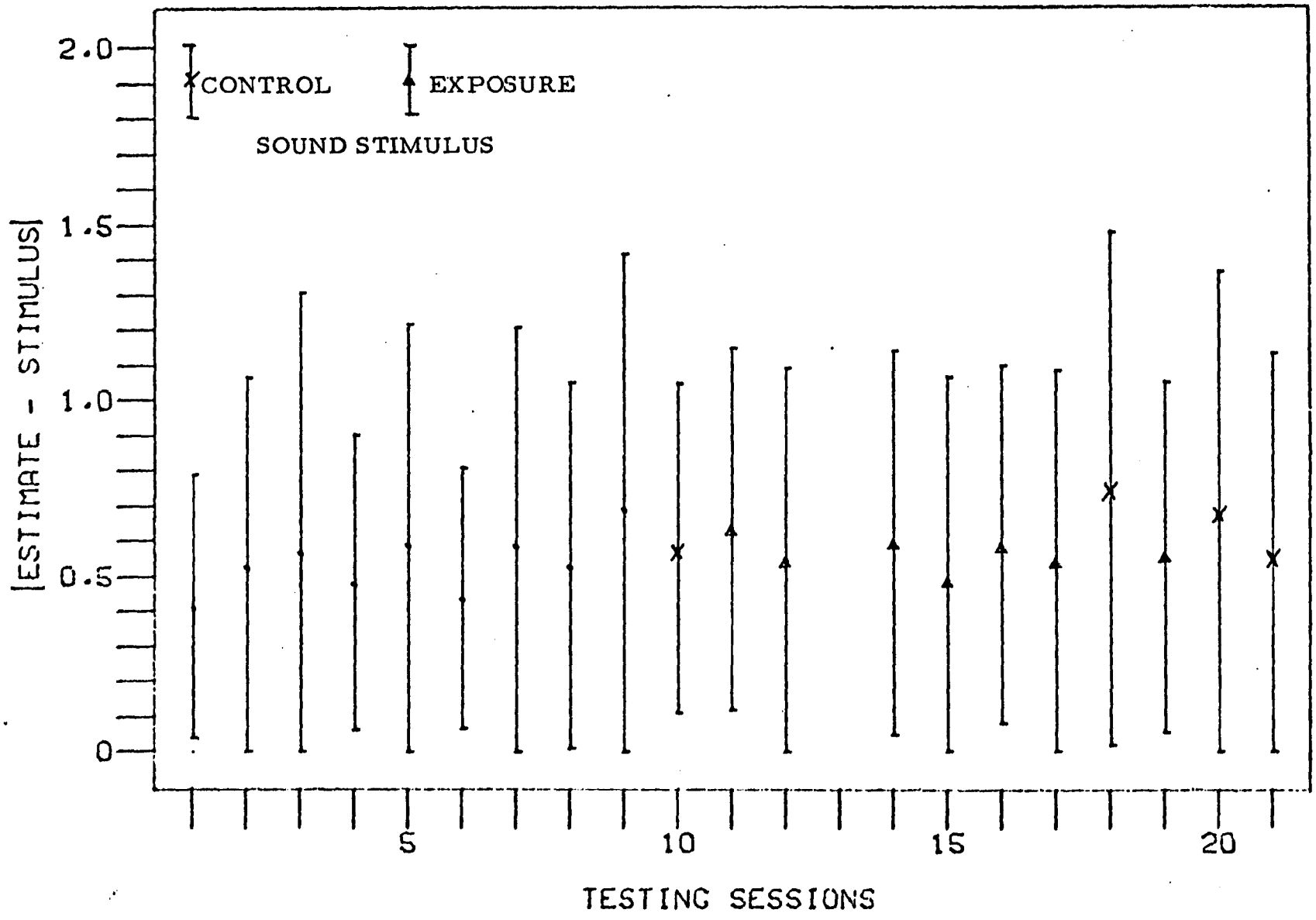


FIGURE 21

EFFECT OF TRAINING AND EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - 3 HOUR SUBJECTS

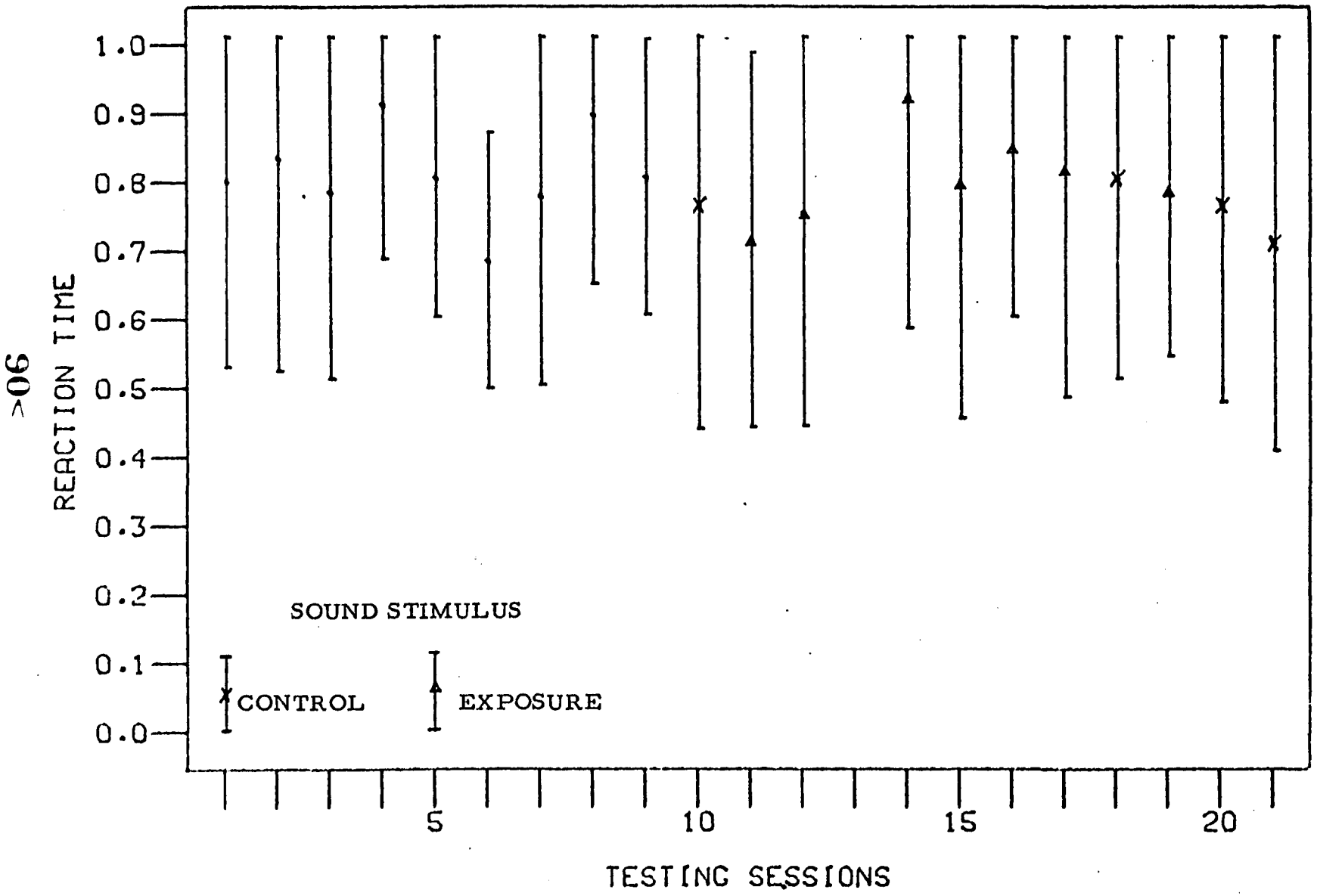


FIGURE 22

EFFECT OF TRAINING AND EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - 3 HOUR SUBJECTS

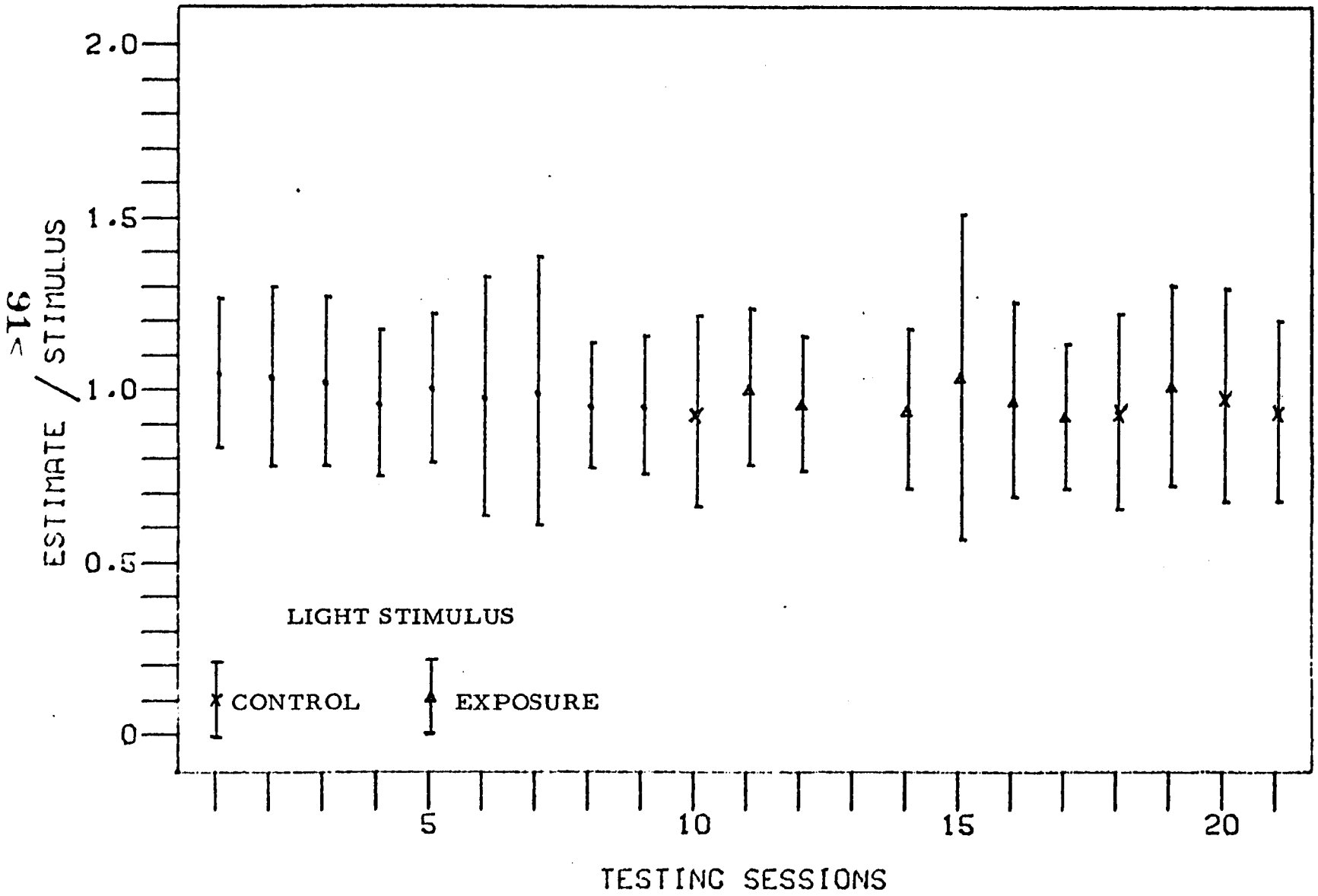


FIGURE 23

EFFECT OF TRAINING AND EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - 3 HOUR SUBJECTS

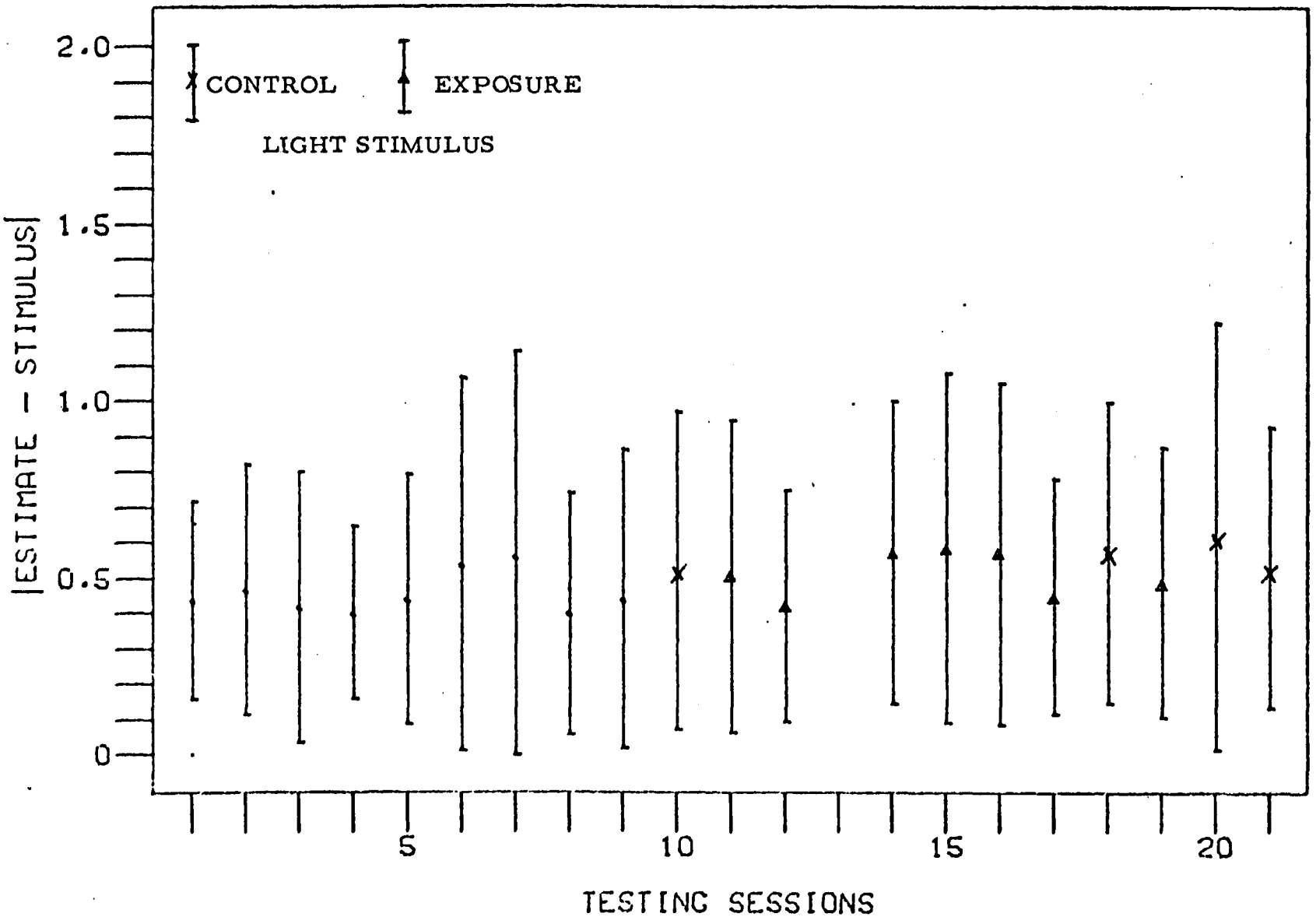


FIGURE 24

EFFECT OF TRAINING AND EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - 3 HOUR SUBJECTS

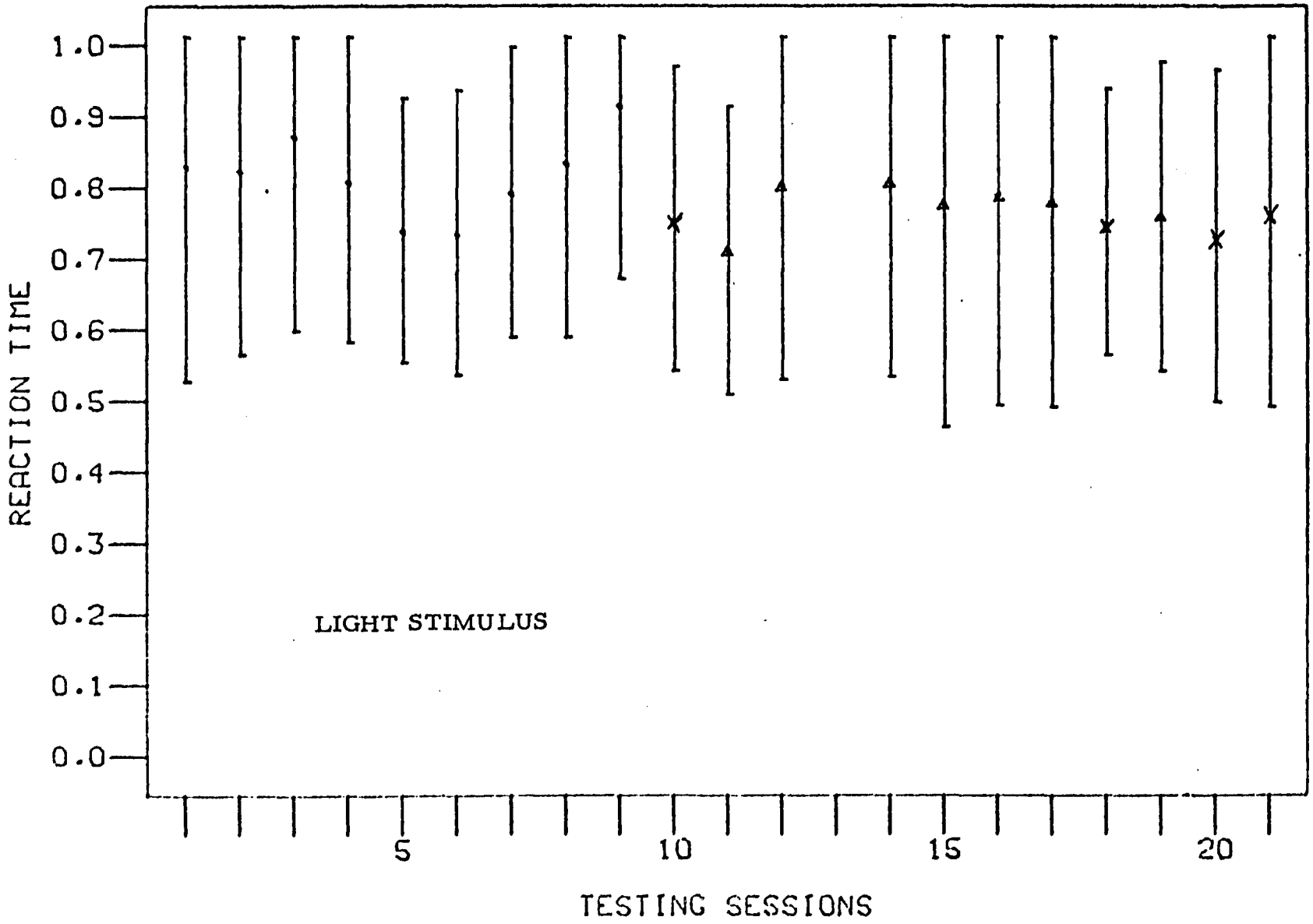


FIGURE 25

EFFECT OF TRAINING AND EXPOSURE TO TOLUENE

ON THE ARITHMETIC TEST - 3 HOUR SUBJECTS

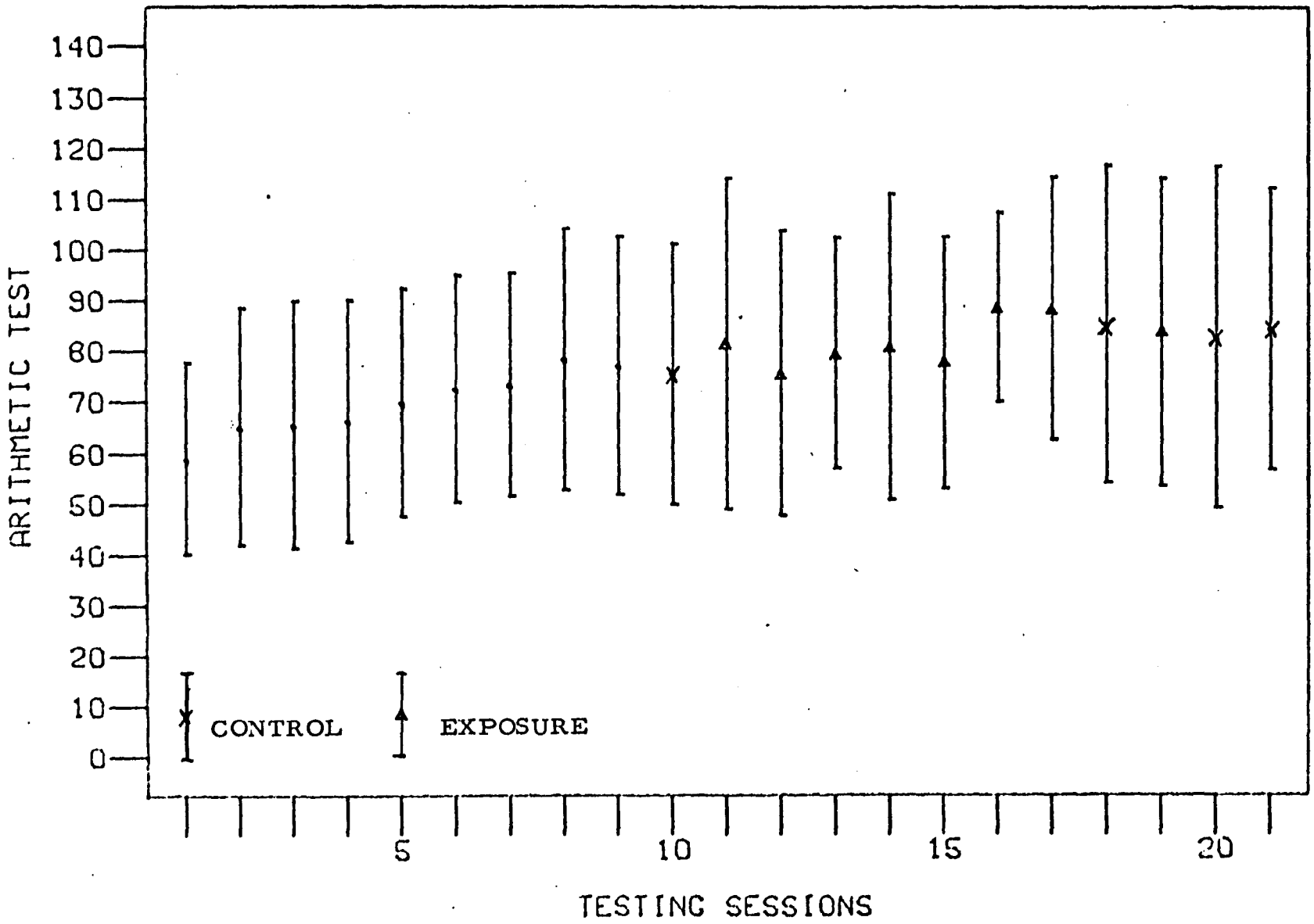


FIGURE 26

EFFECT OF TRAINING AND EXPOSURE TO TOLUENE

ON THE COORDINATION TEST - 3 HOUR SUBJECTS

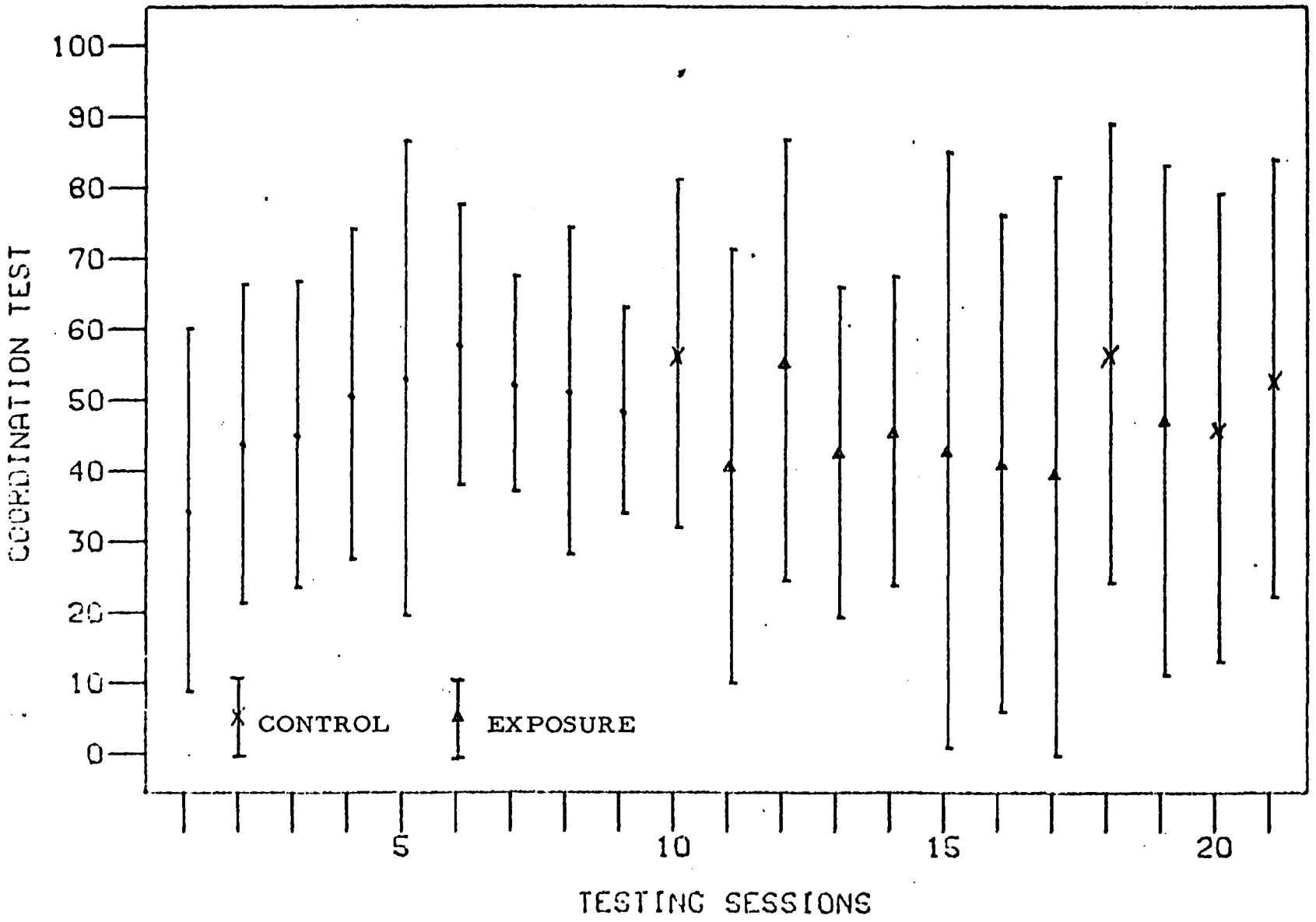


FIGURE 27

EFFECT OF TRAINING AND EXPOSURE TO TOLUENE

ON THE INSPECTION TEST - 3 HOUR SUBJECTS

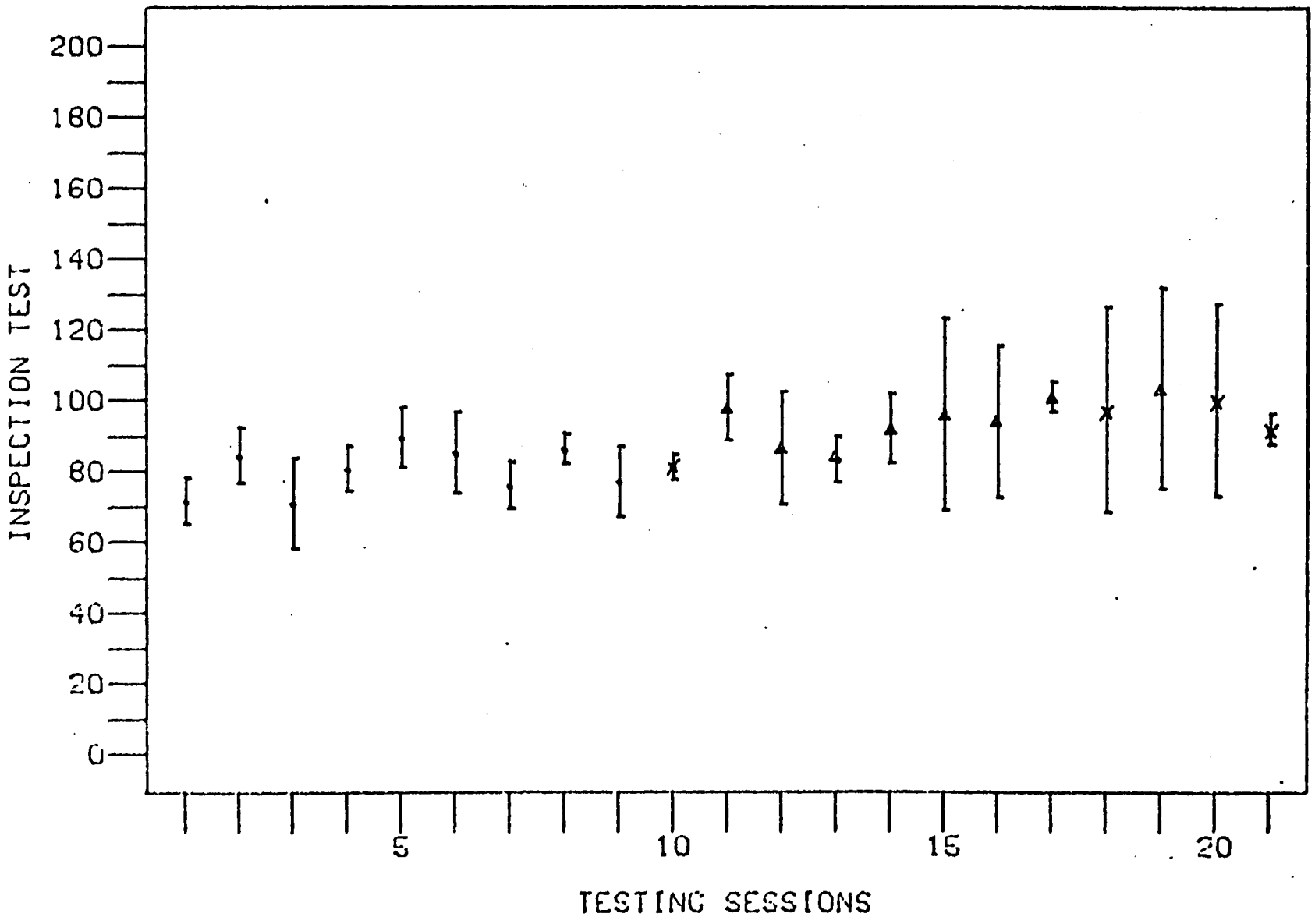


FIGURE 28

EFFECT OF EXPOSURE TO TOLUENE

ON TIME ESTIMATIONS - 7 1/2 HOUR SUBJECTS

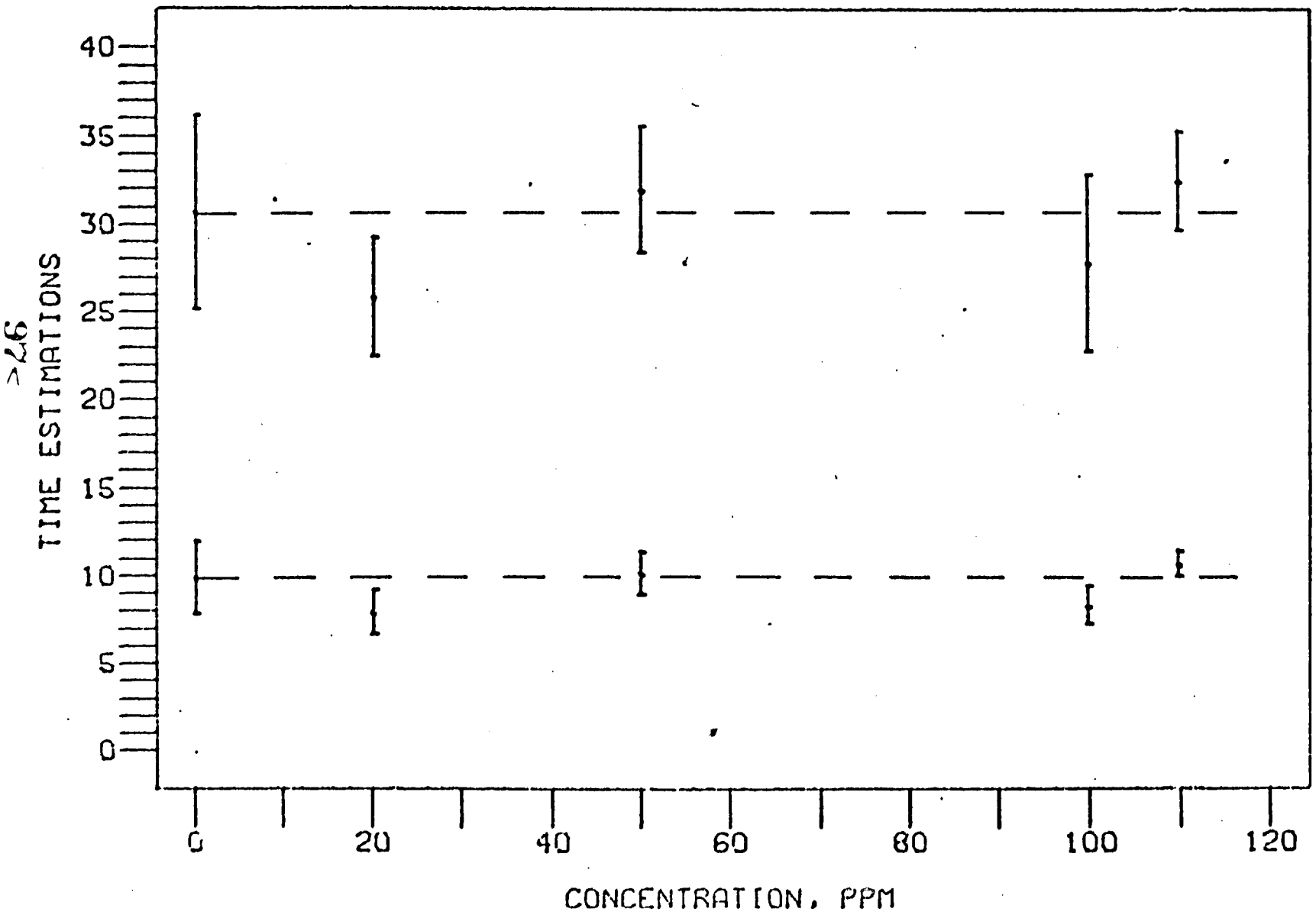


FIGURE 29

EFFECT OF EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - 7 1/2 HOUR SUBJECTS

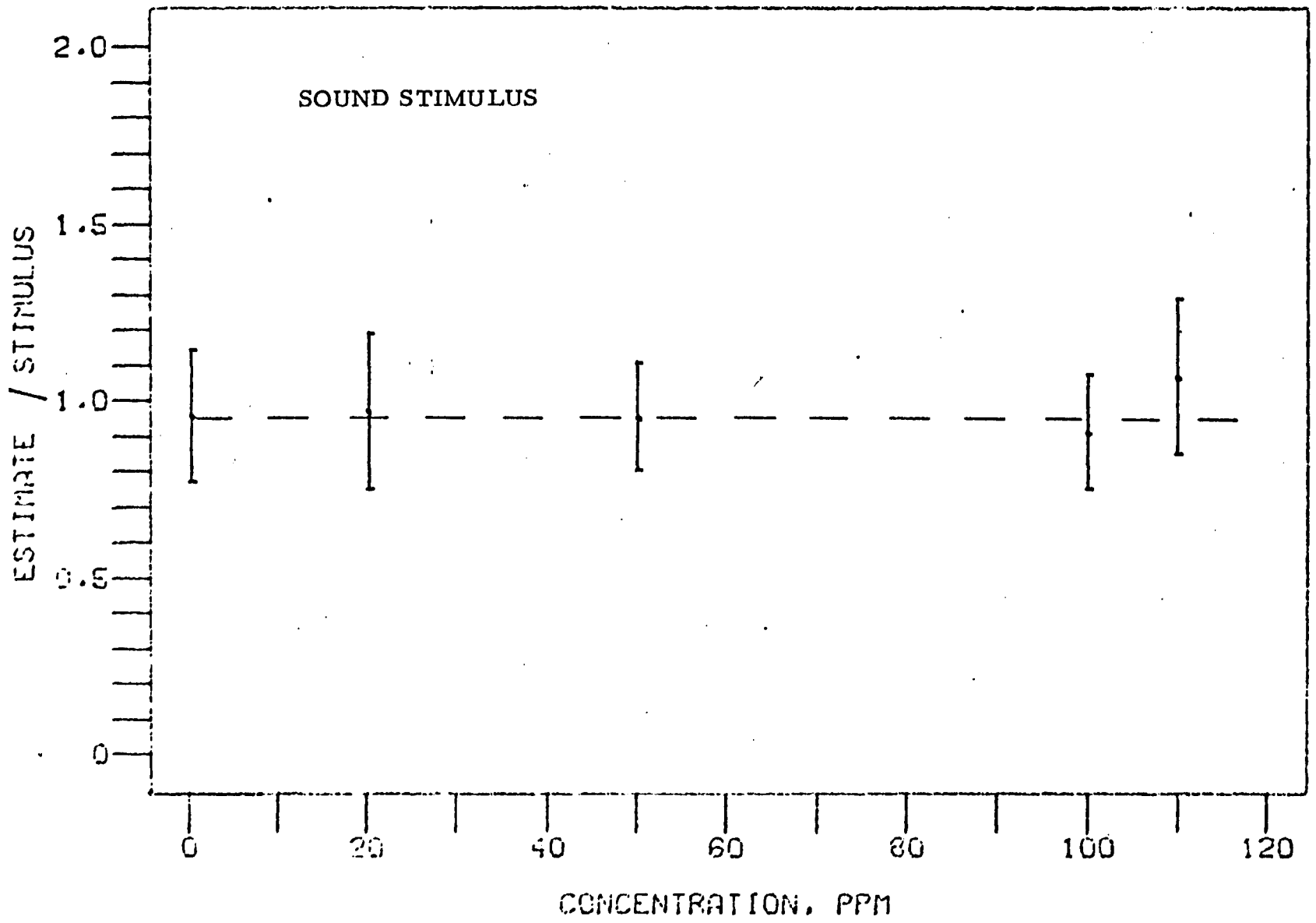


FIGURE 30

EFFECT OF EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - 7 1/2 HOUR SUBJECTS

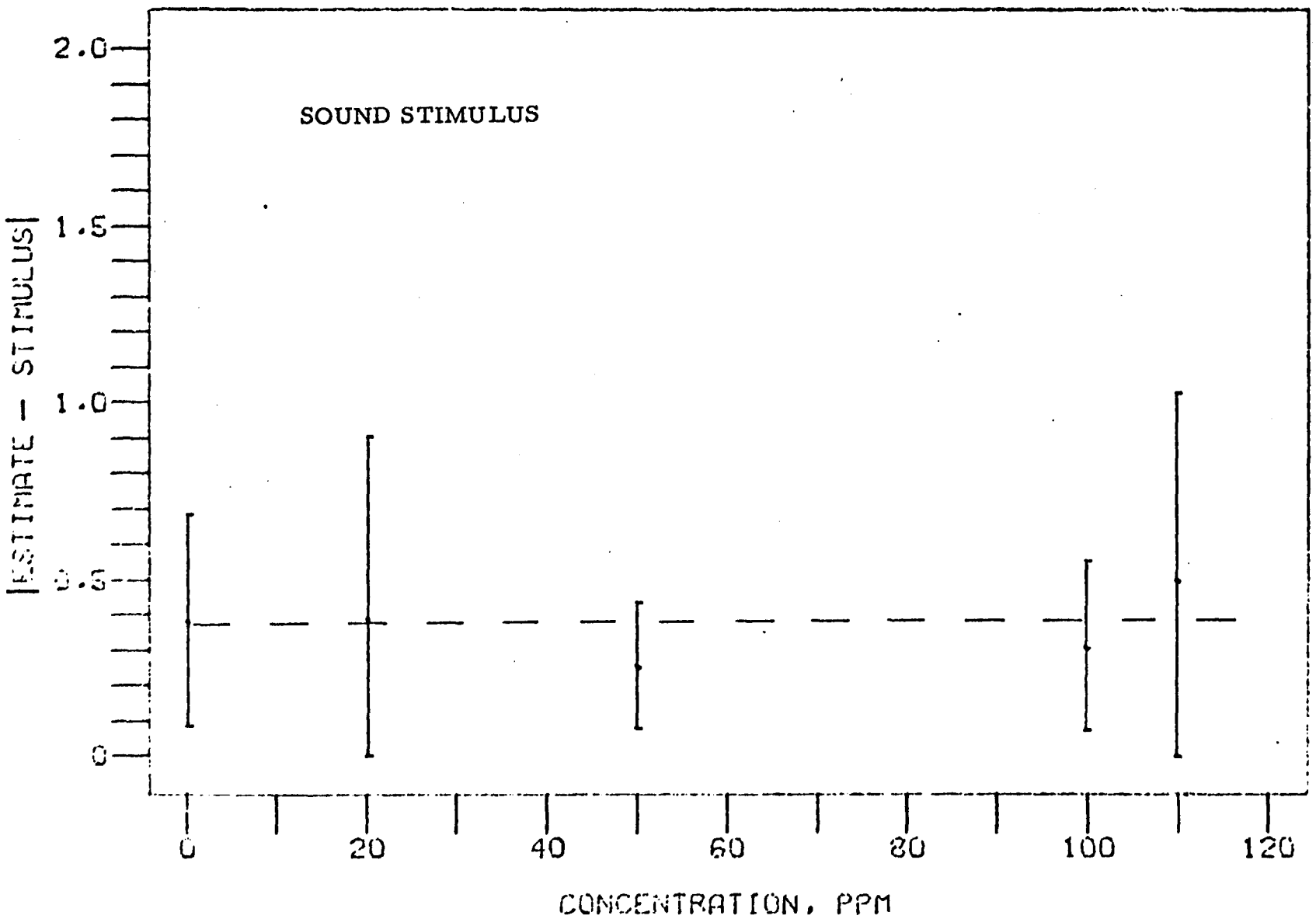
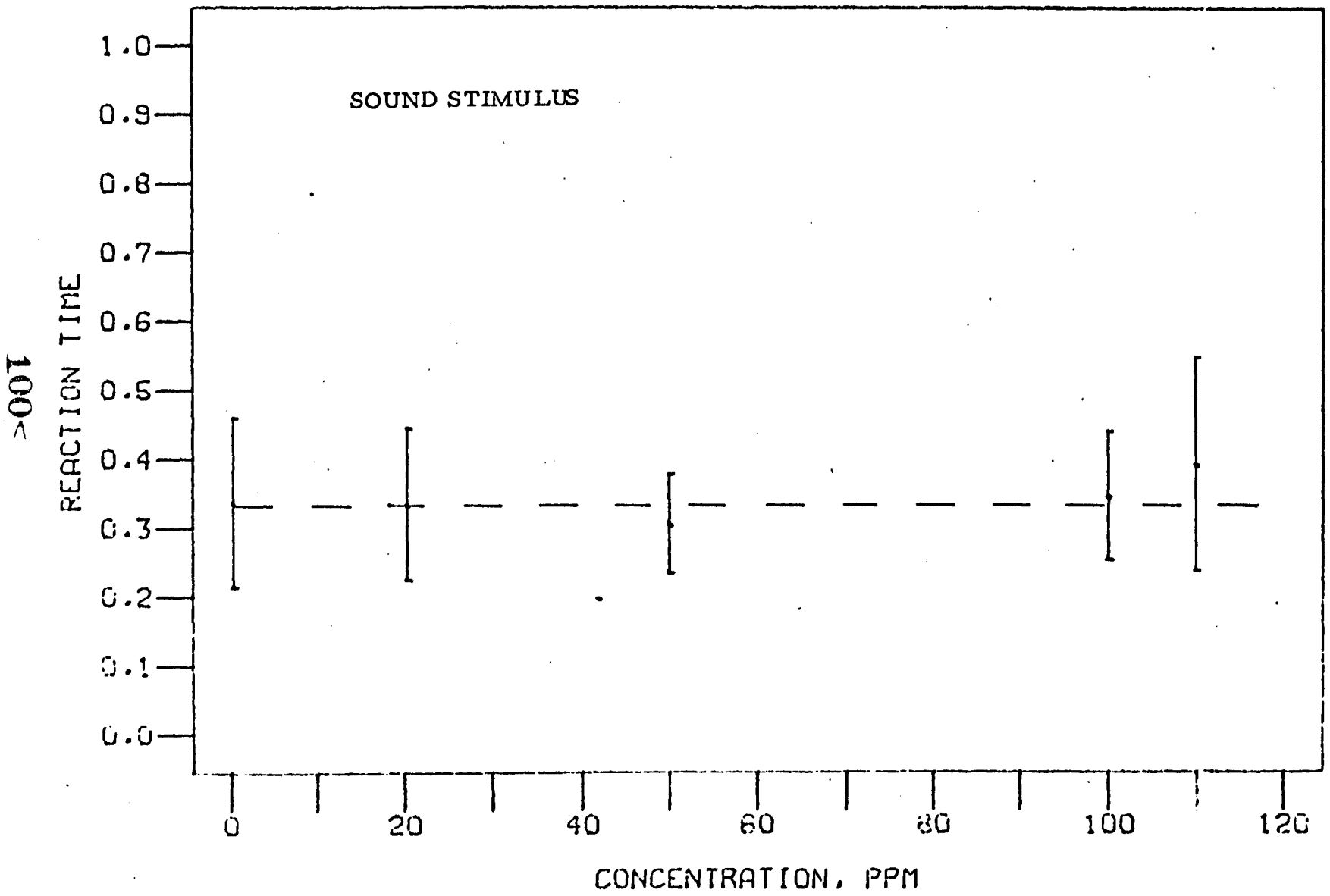


FIGURE 31

EFFECT OF EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - 7 1/2 HOUR SUBJECTS



100<

FIGURE 32

EFFECT OF EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - 7 1/2 HOUR SUBJECTS

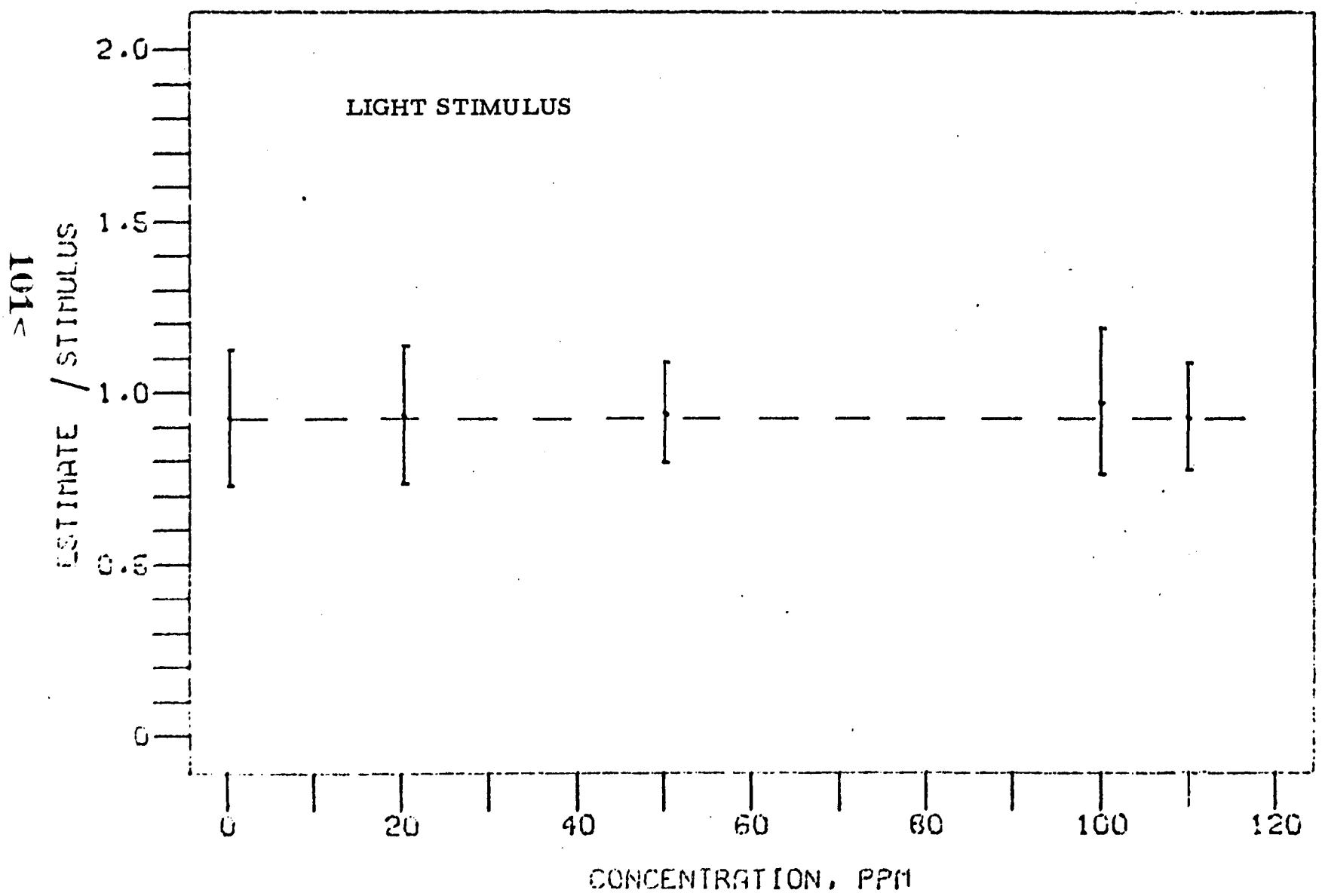


FIGURE 33

EFFECT OF EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - 7 1/2 HOUR SUBJECTS

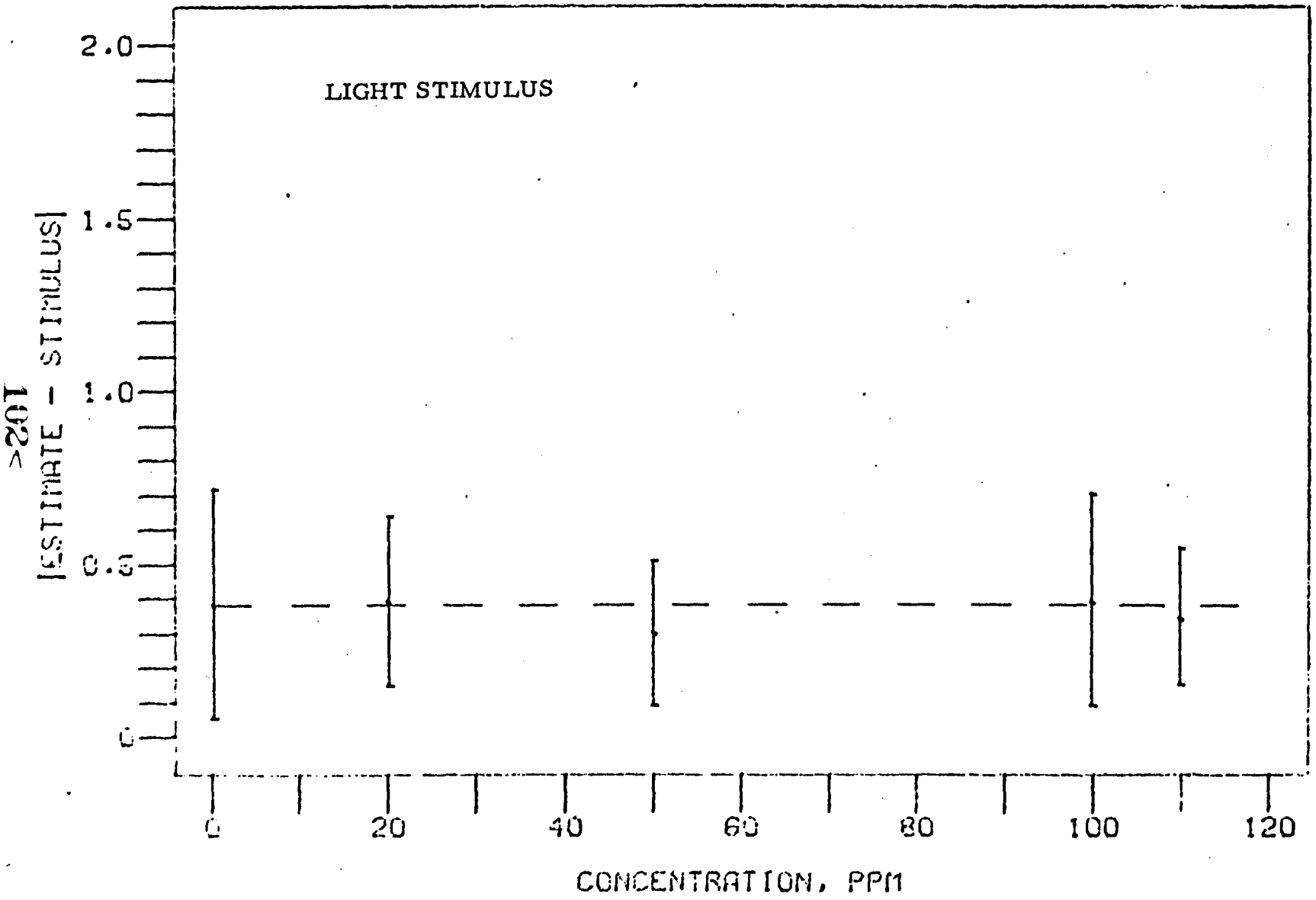


FIGURE 34

EFFECT OF EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - 7 1/2 HOUR SUBJECTS

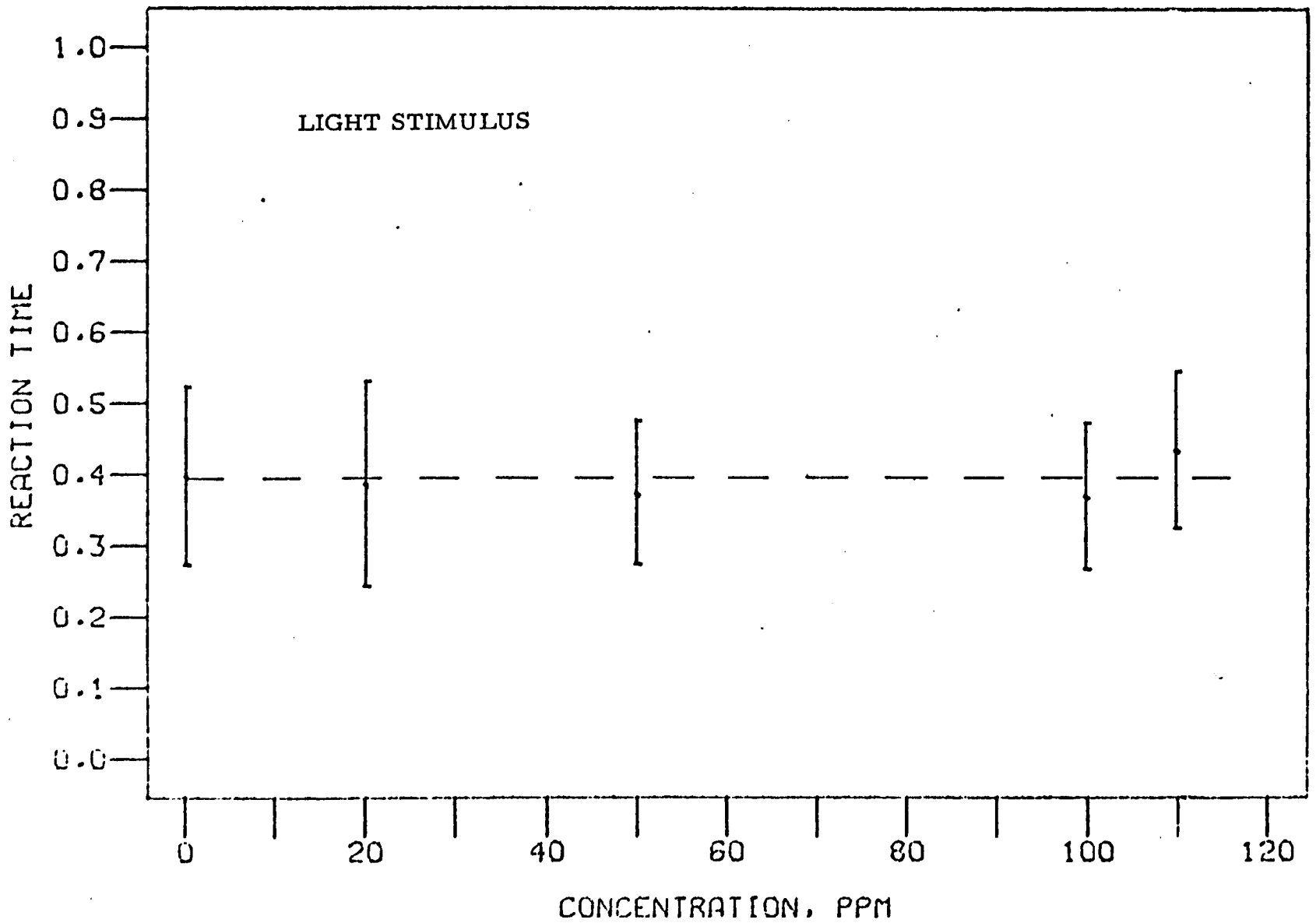


FIGURE 35

EFFECT OF EXPOSURE TO TOLUENE

ON THE ARITHMETIC TEST - 7 1/2 HOUR SUBJECTS

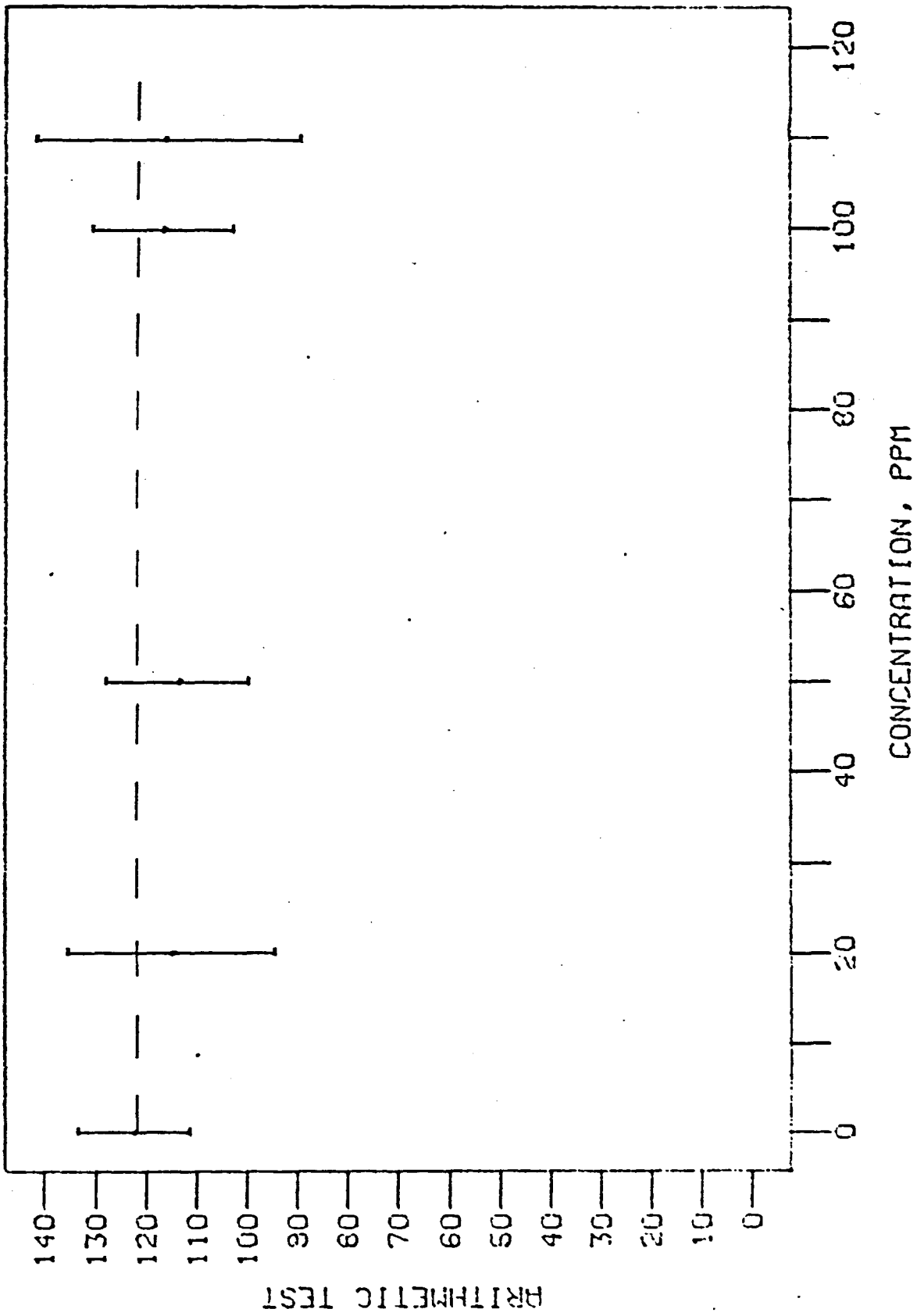


FIGURE 36

EFFECT OF EXPOSURE TO TOLUENE

ON THE COORDINATION TEST - 7 1/2 HOUR SUBJECTS

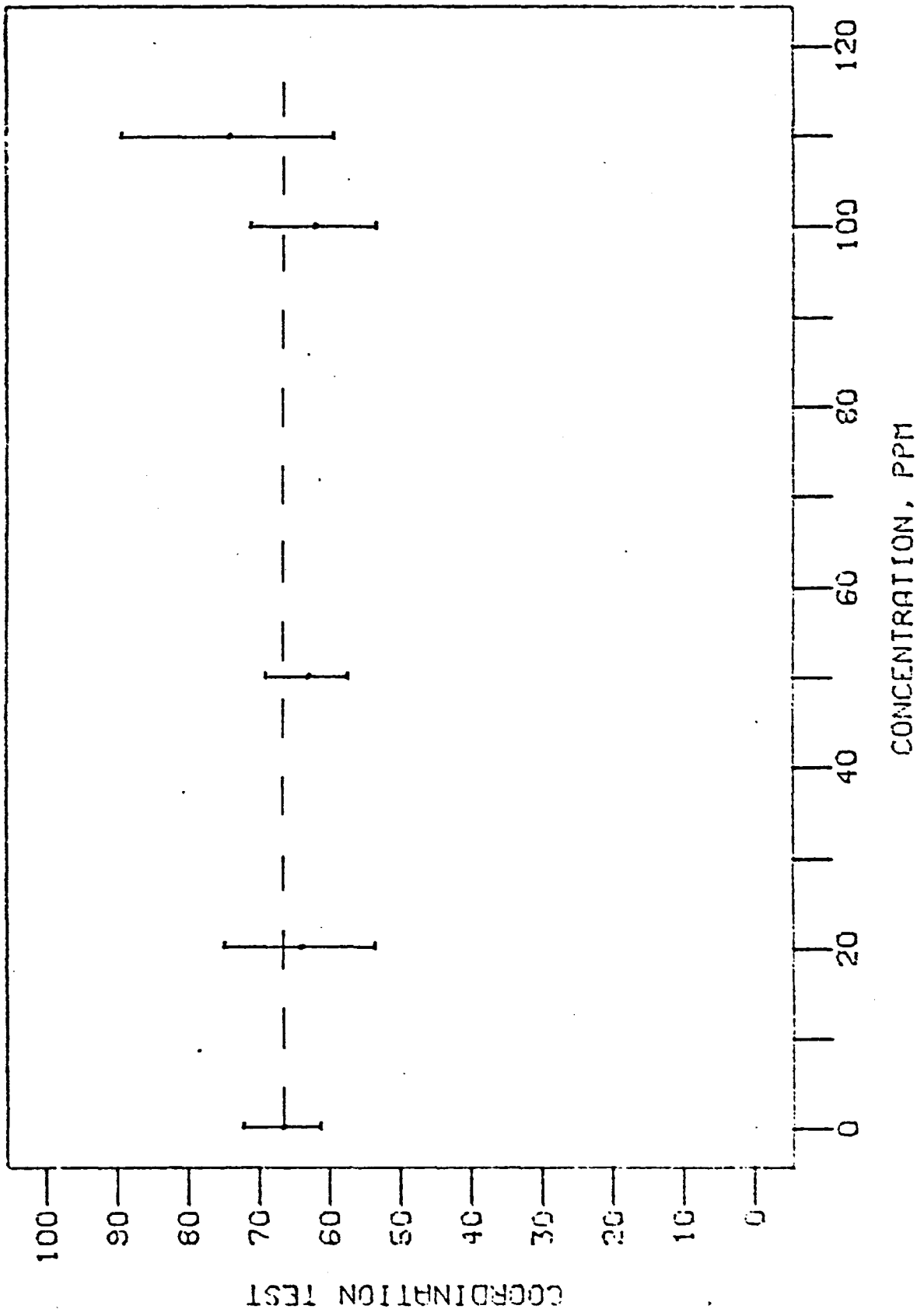


FIGURE 37

EFFECT OF EXPOSURE TO TOLUENE

ON THE INSPECTION TEST - 7 1/2 HOUR SUBJECTS

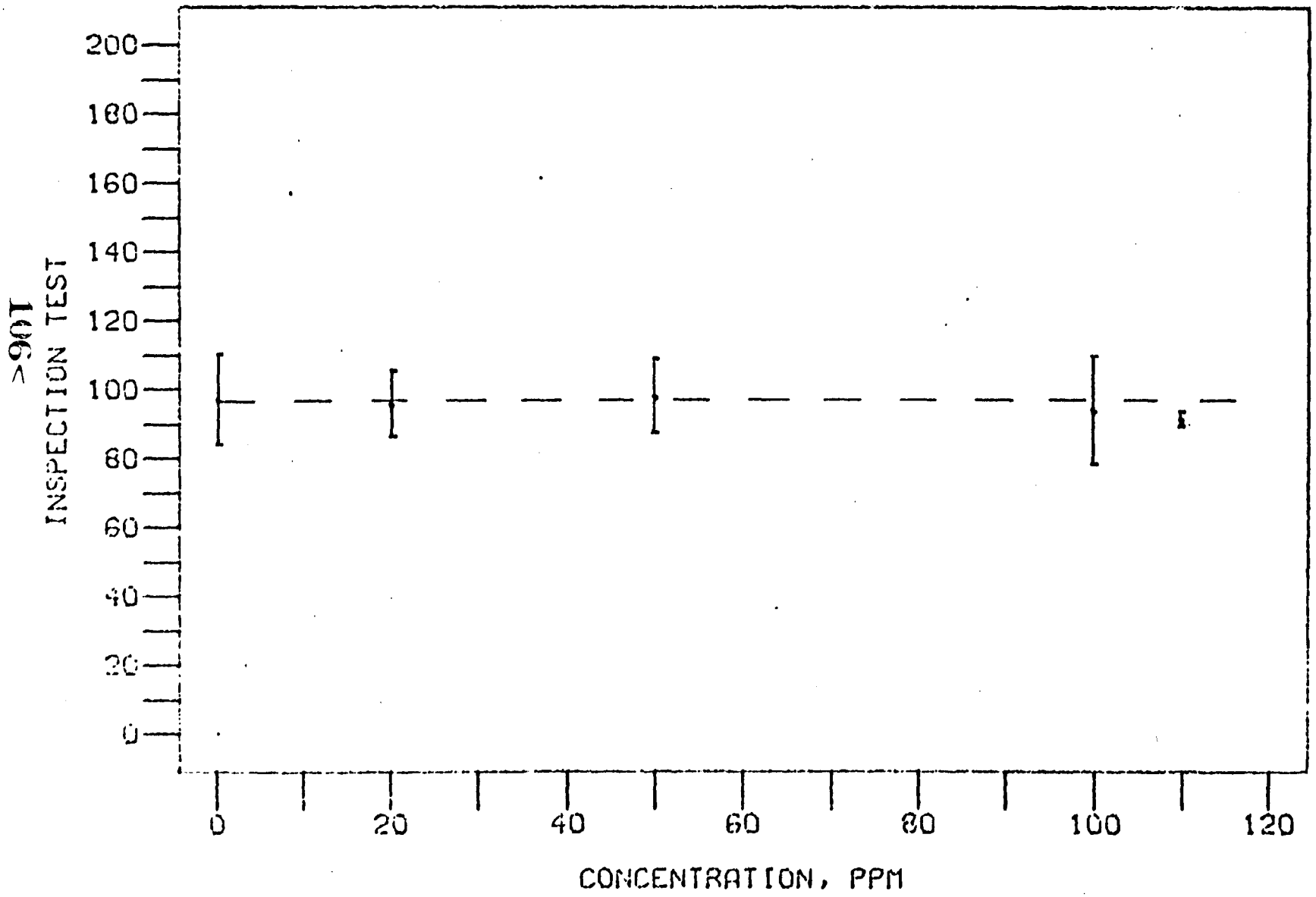


FIGURE 38

EFFECT OF EXPOSURE TO TOLUENE

ON TIME ESTIMATIONS - 3 HOUR SUBJECTS

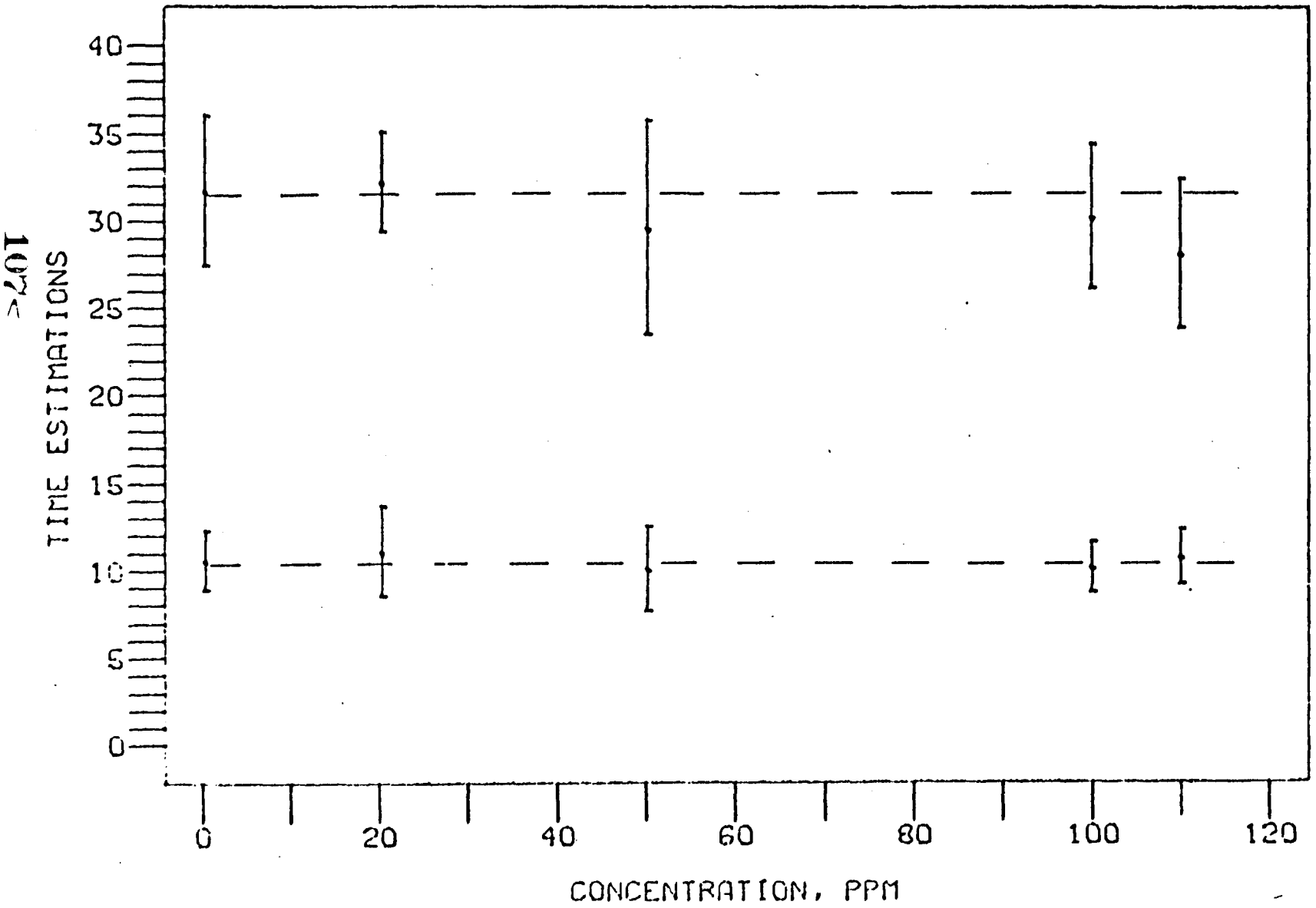


FIGURE 39

EFFECT OF EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - 3 HOUR SUBJECTS

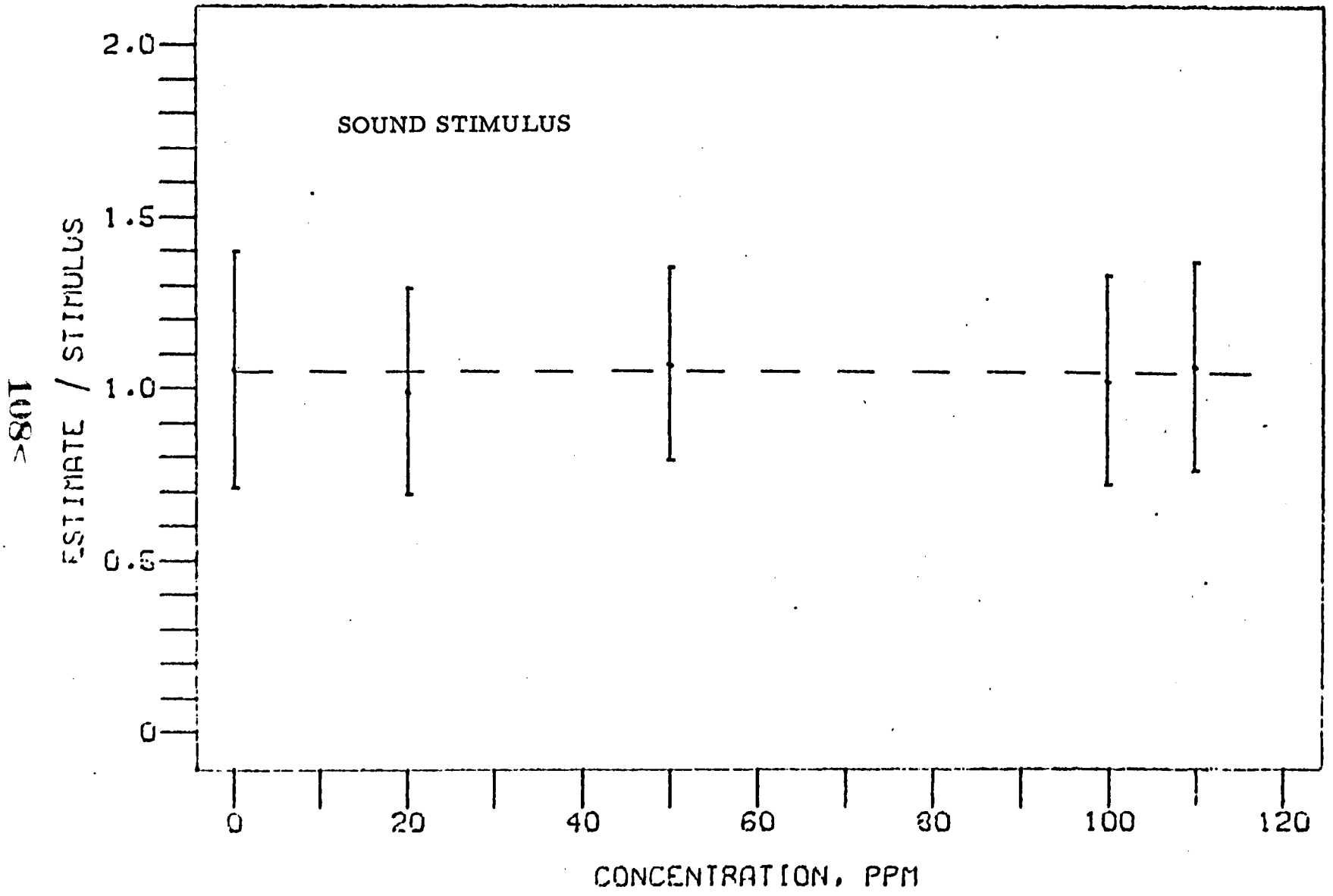


FIGURE 40

EFFECT OF EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - 3 HOUR SUBJECTS

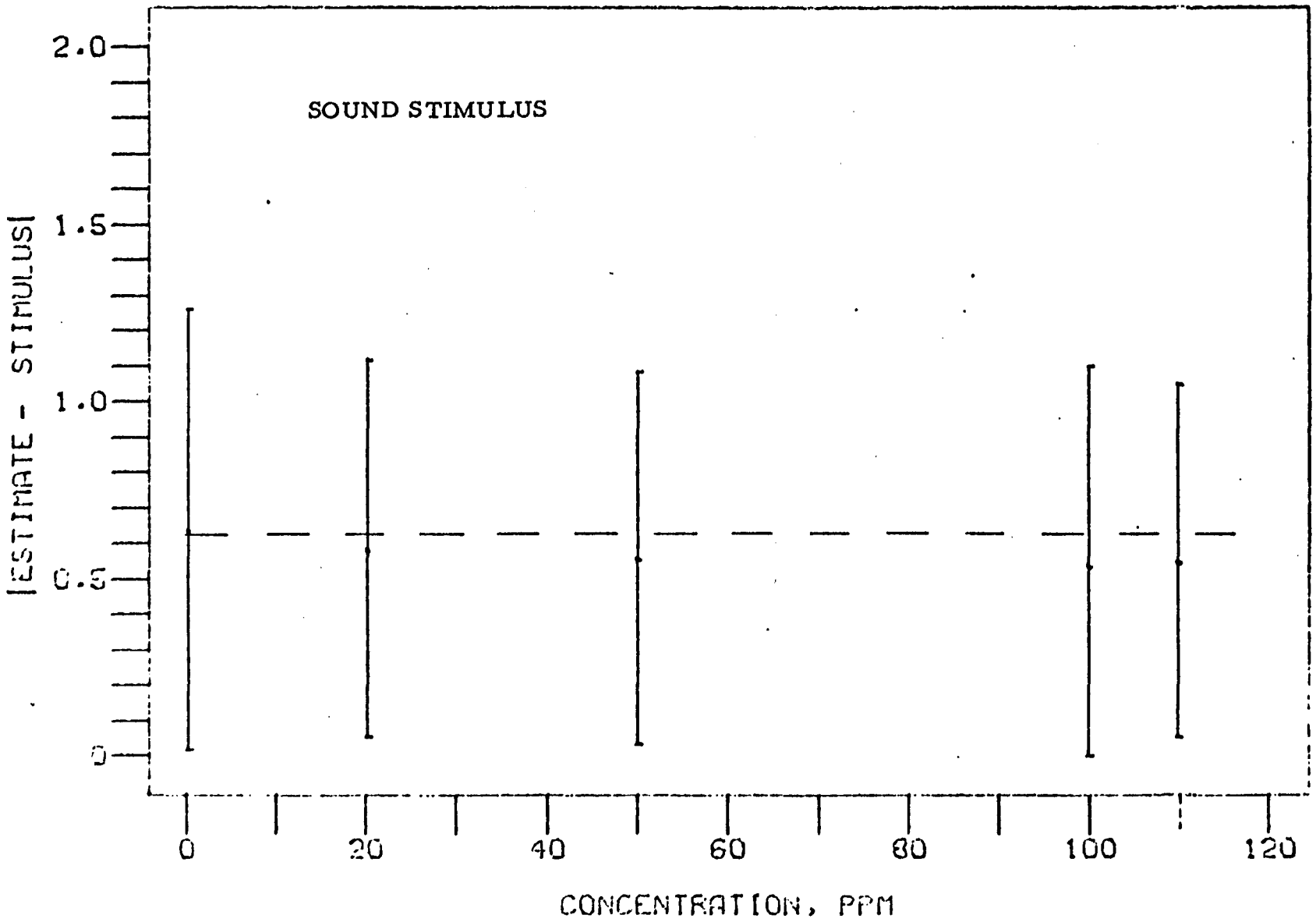


FIGURE 41

EFFECT OF EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - 3 HOUR SUBJECTS

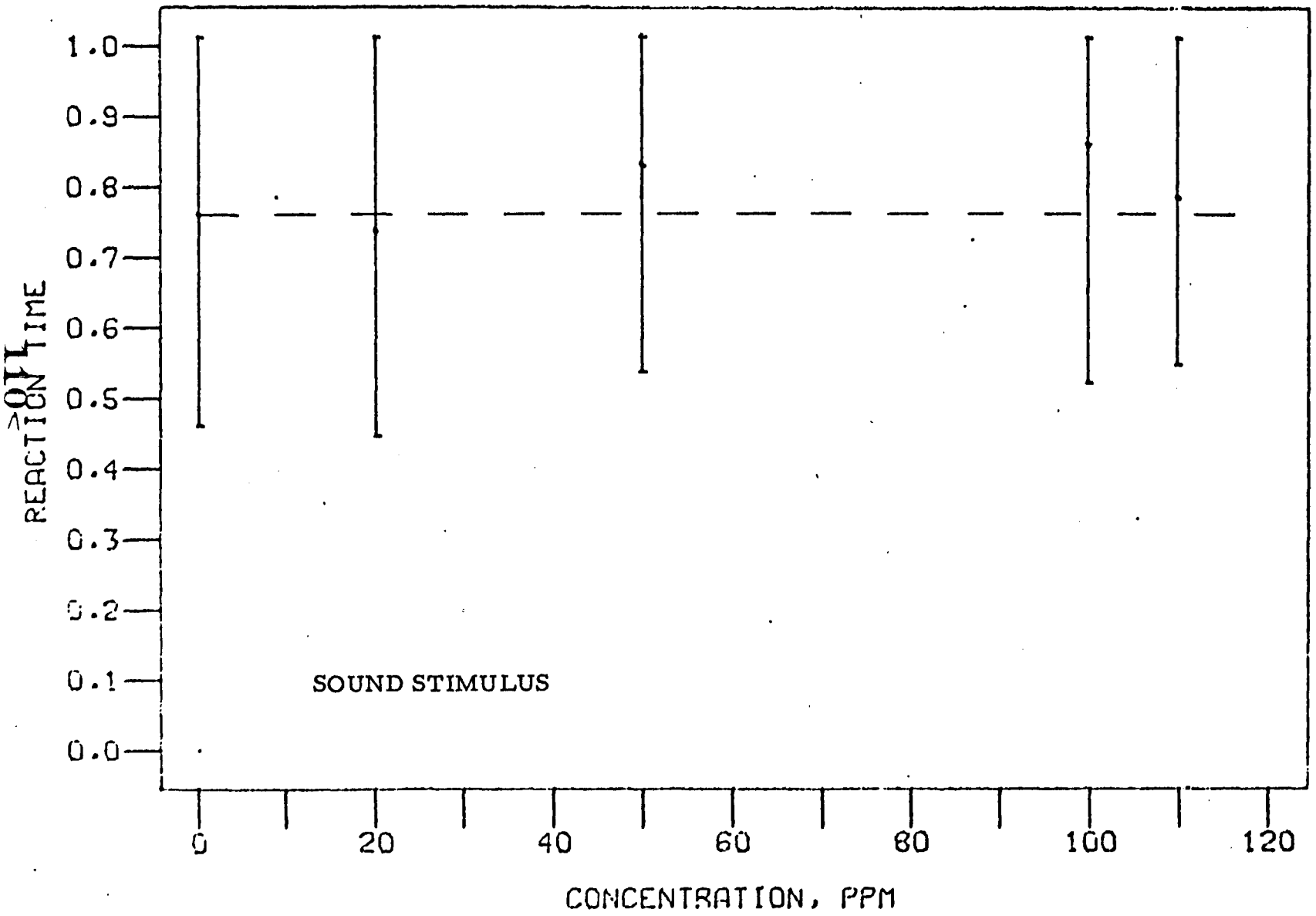


FIGURE 42

EFFECT OF EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - 3 HOUR SUBJECTS

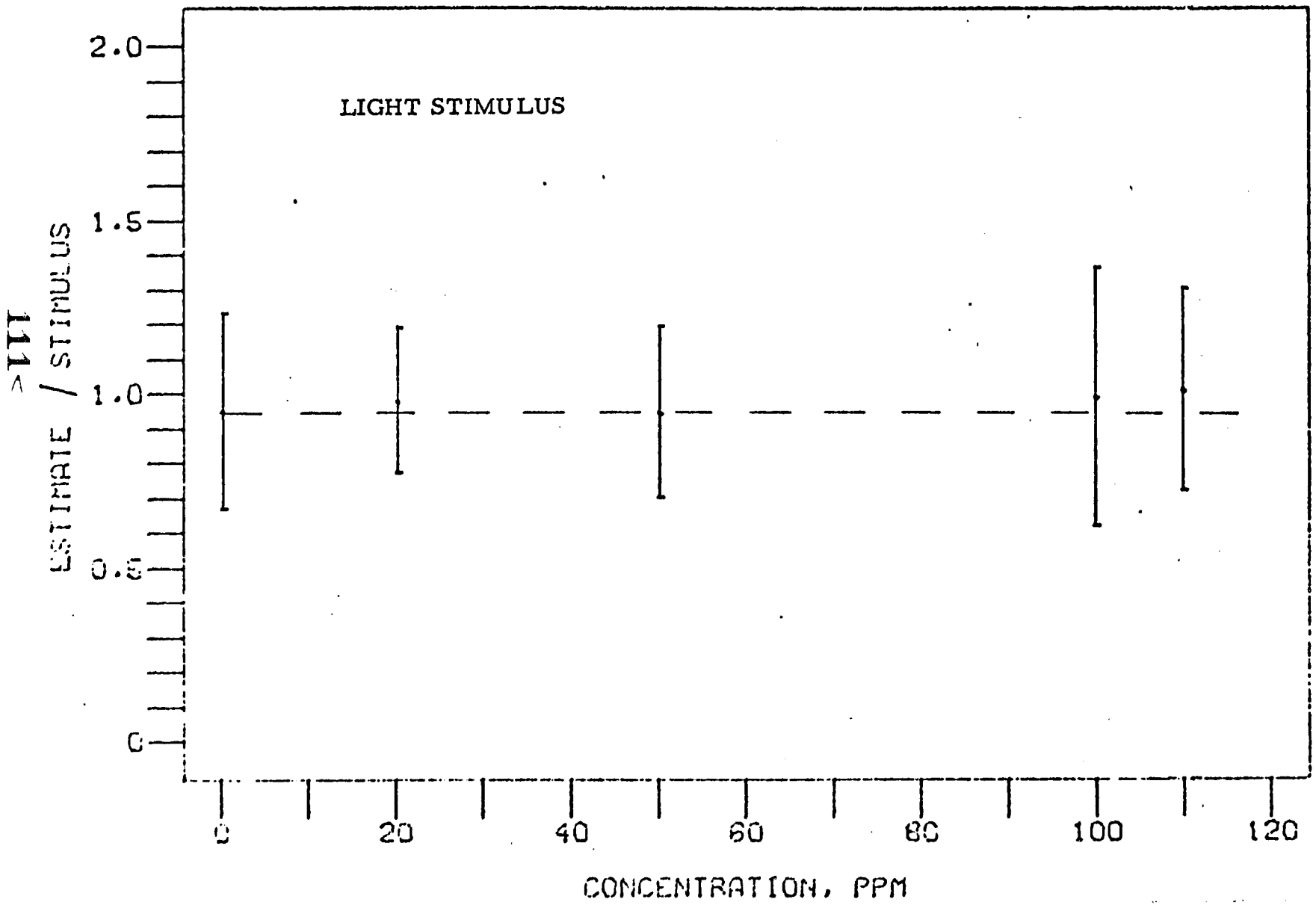


FIGURE 43

EFFECT OF EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - 3 HOUR SUBJECTS

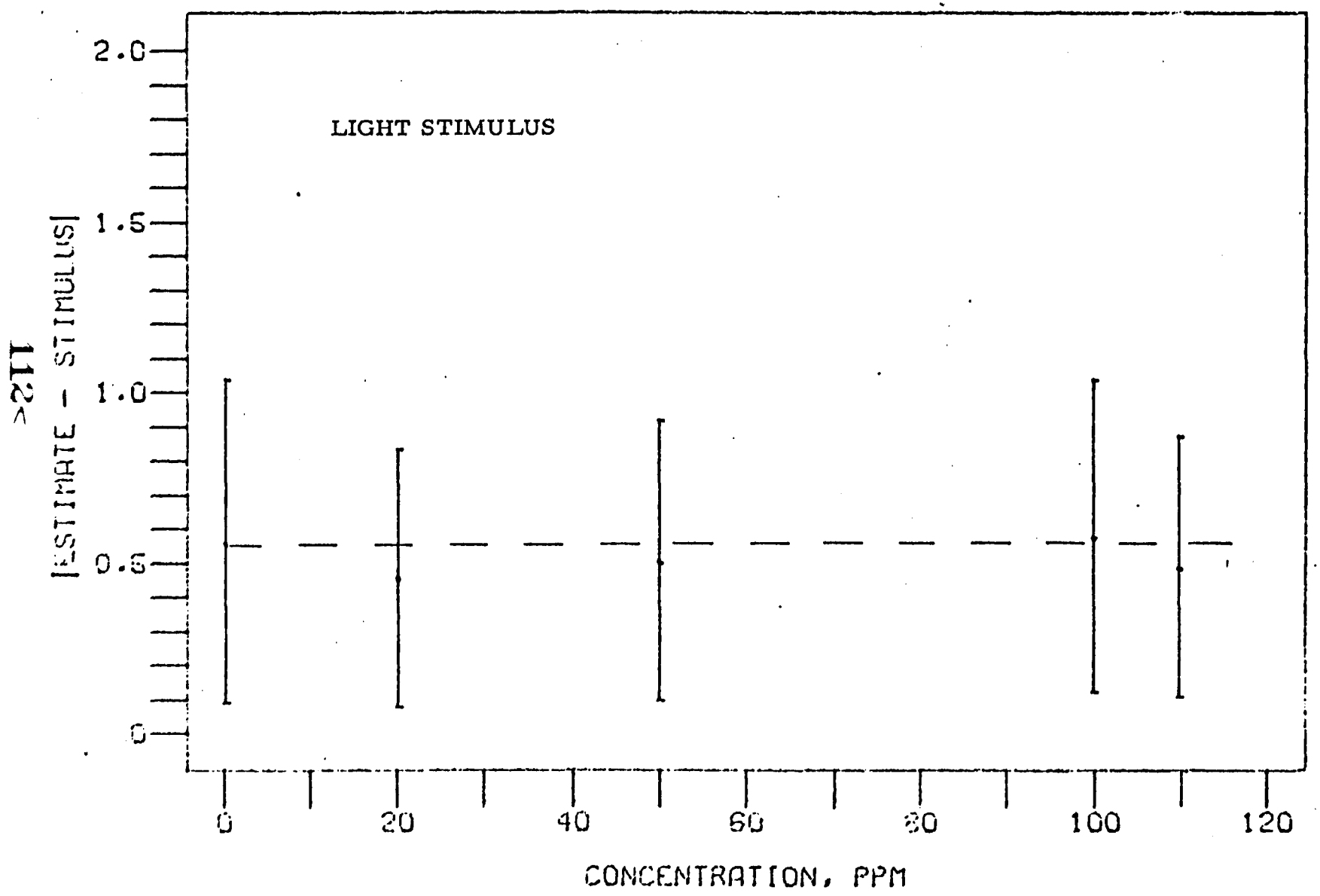


FIGURE 44

EFFECT OF EXPOSURE TO TOLUENE

ON THE MARQUETTE TEST - 3 HOUR SUBJECTS

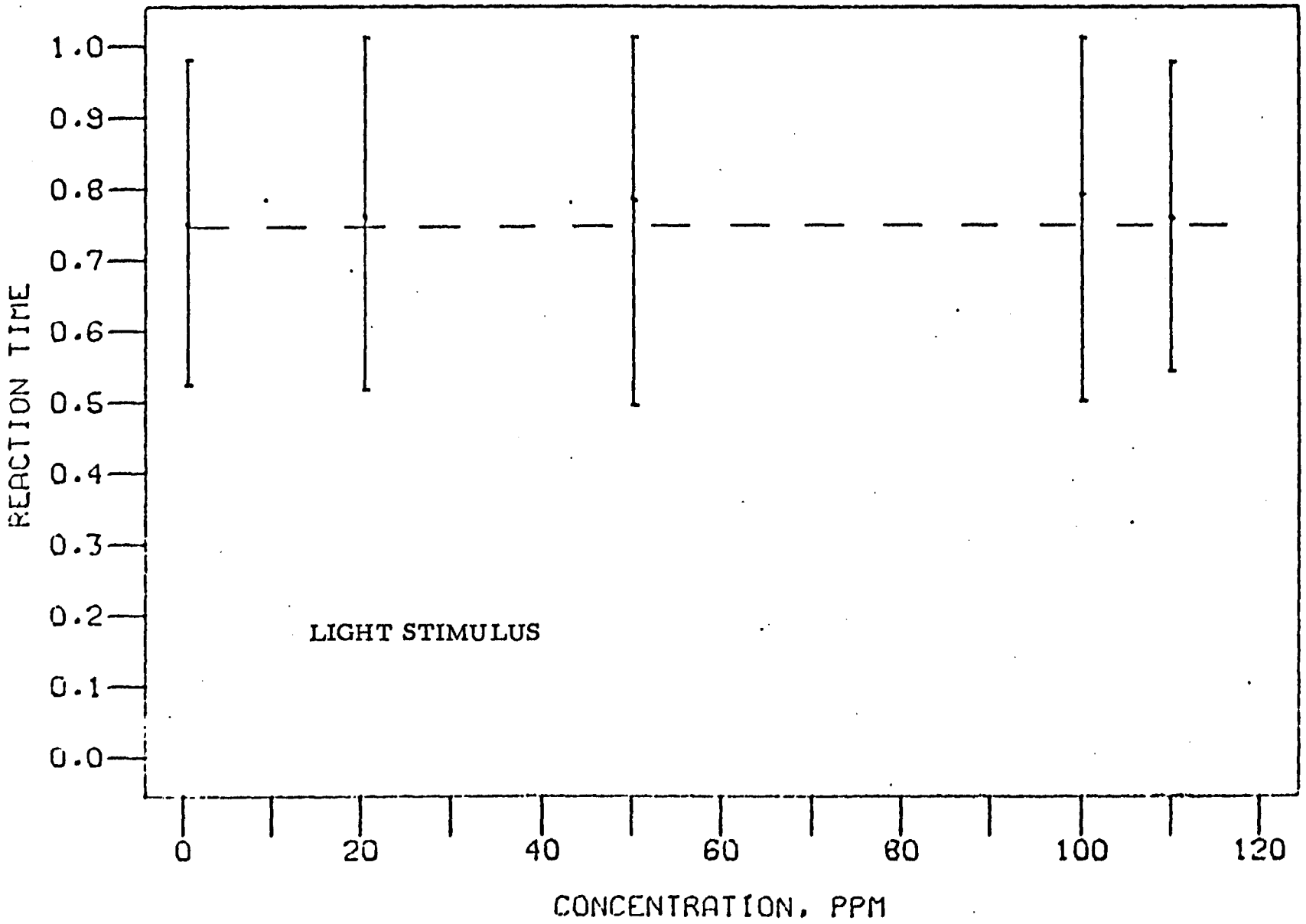


FIGURE 45

EFFECT OF EXPOSURE TO TOLUENE

ON THE ARITHMETIC TEST - 3 HOUR SUBJECTS

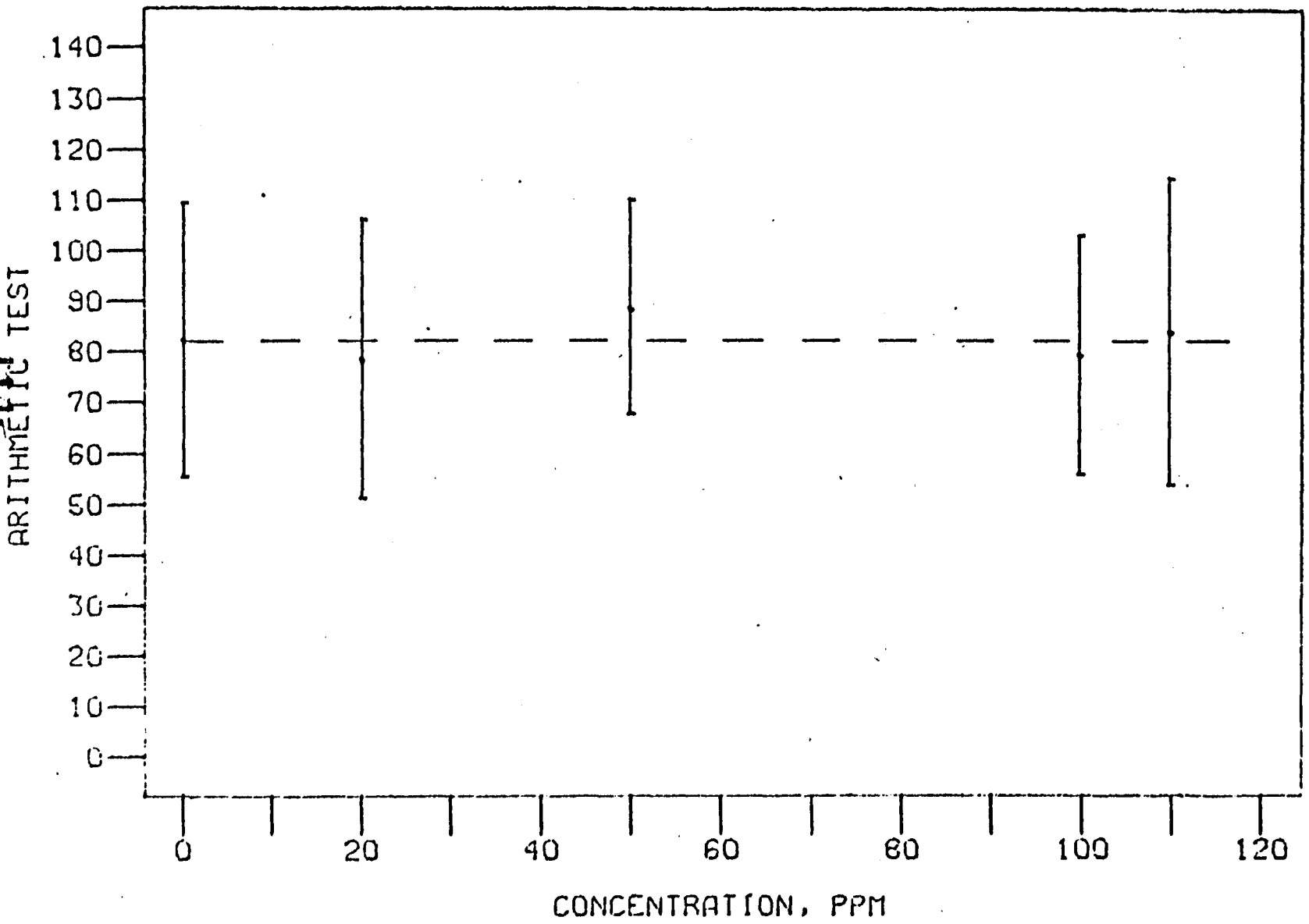


FIGURE 46

EFFECT OF EXPOSURE TO TOLUENE

ON THE COORDINATION TEST - 3 HOUR SUBJECTS

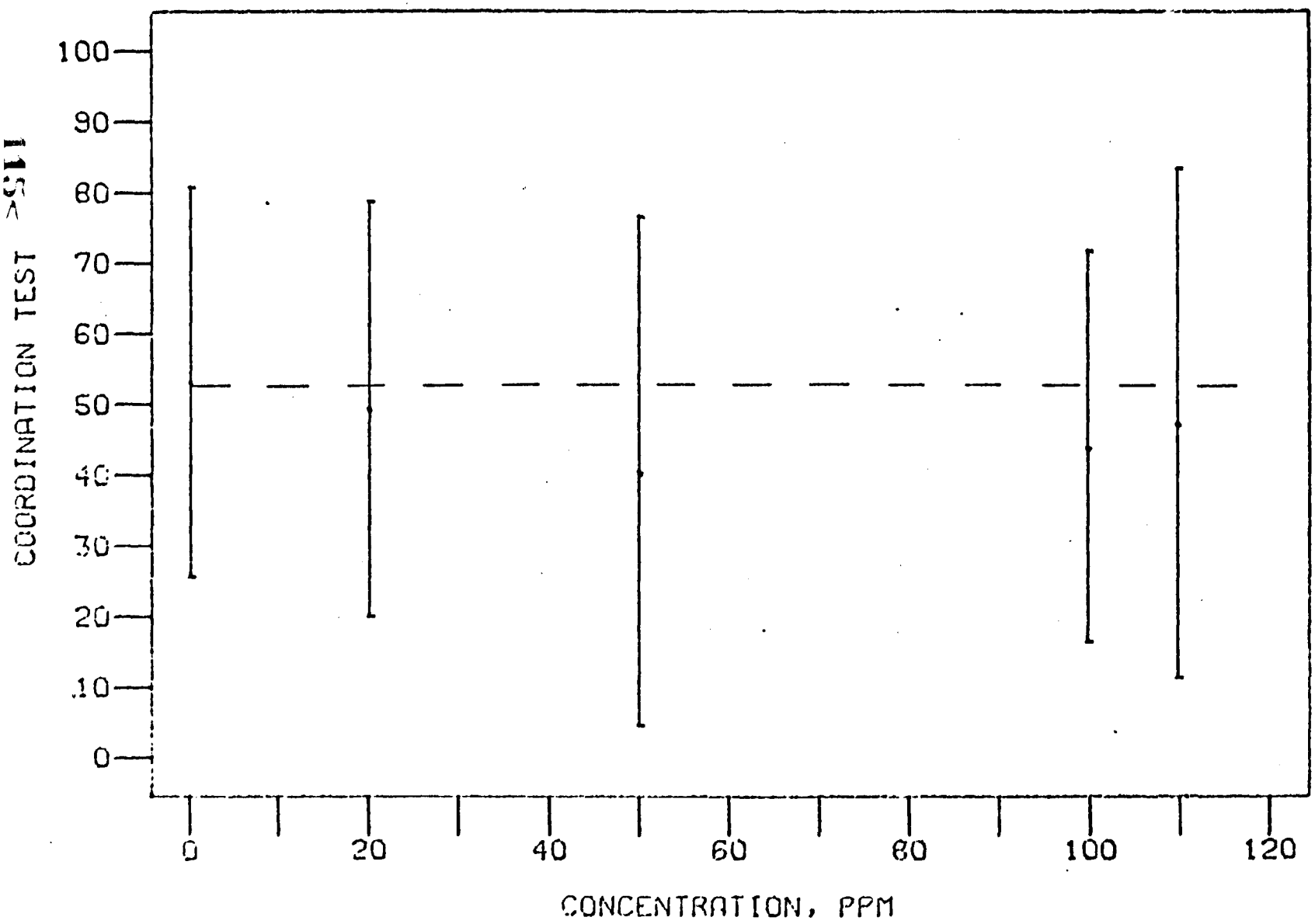


FIGURE 47

EFFECT OF EXPOSURE TO TOLUENE

ON THE INSPECTION TEST - 3 HOUR SUBJECTS

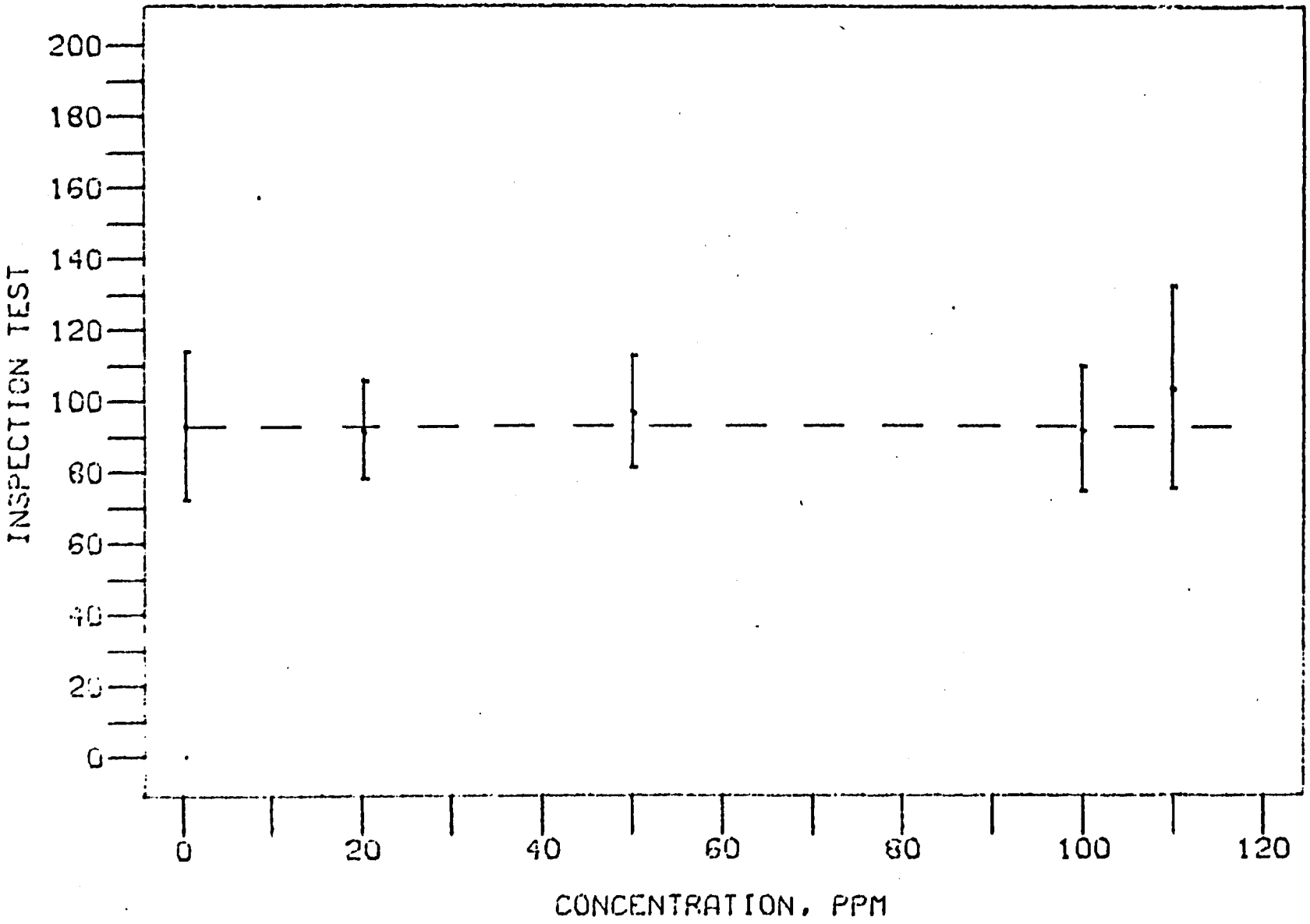


FIGURE 48

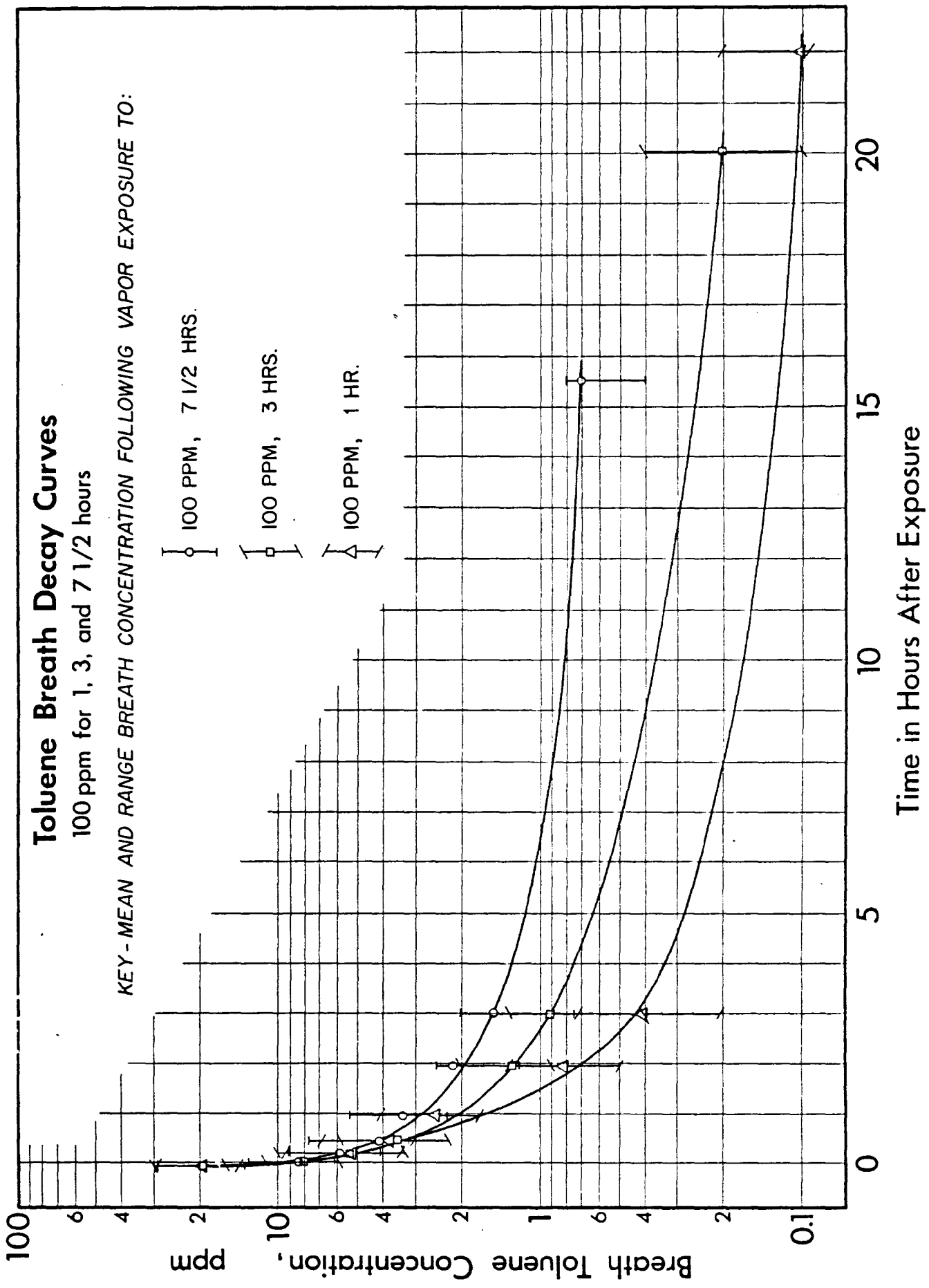

Toluene Breath Decay Curves
100 ppm for 1, 3, and 7 1/2 hours
KEY - MEAN AND RANGE BREATH CONCENTRATION FOLLOWING VAPOR EXPOSURE TO:
100 PPM, 7 1/2 HRS.
100 PPM, 3 HRS.
100 PPM, 1 HR.
Breath Toluene Concentration, ppm
100
6
4
2
10
6
4
2
1
6
4
2
0.1
0
5
10
15
20
Time in Hours After Exposure

FIGURE 49

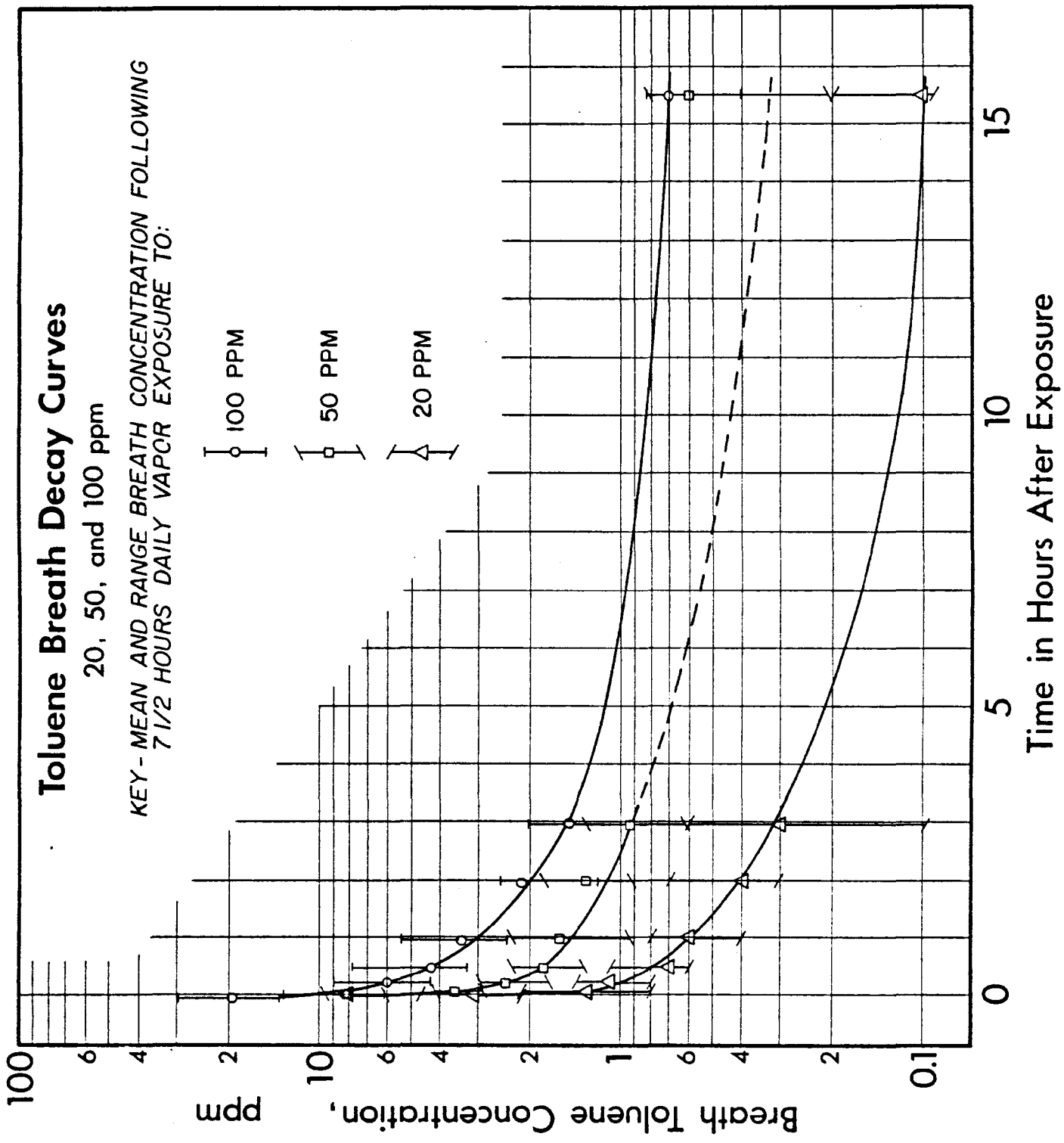
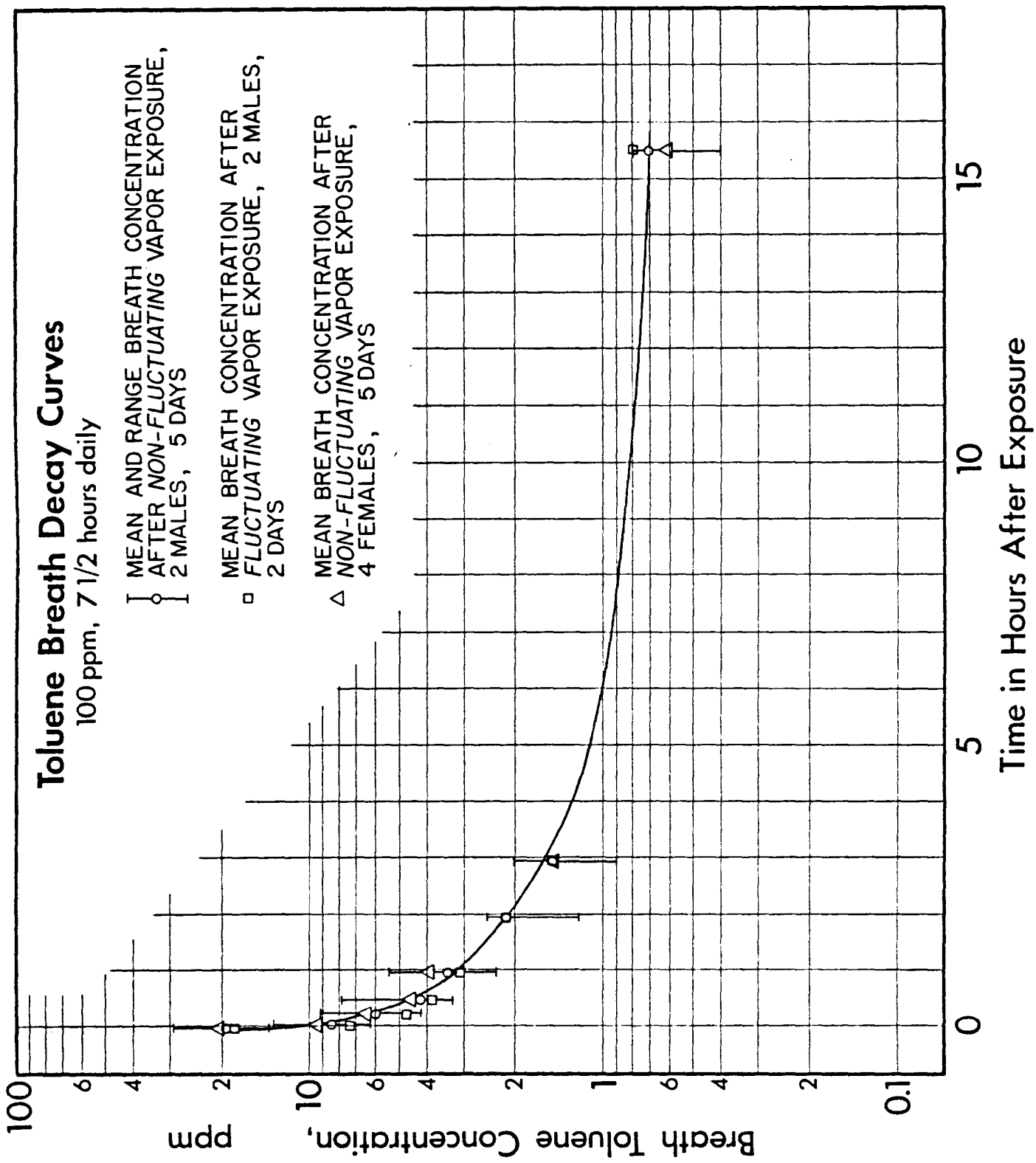

Toluene Breath Decay Curves
20, 50, and 100 ppm
KEY - MEAN AND RANGE BREATH CONCENTRATION FOLLOWING 7 1/2 HOURS DAILY VAPOR EXPOSURE TO:
100 PPM
50 PPM
20 PPM
Breath Toluene Concentration, ppm
100
6
4
2
10
6
4
2
1
6
4
2
0.1
0
5
10
15
Time in Hours After Exposure

FIGURE 50


Toluene Breath Decay Curves
100 ppm, 7 1/2 hours daily
MEAN AND RANGE BREATH CONCENTRATION AFTER NON-FLUCTUATING VAPOR EXPOSURE, 2 MALES, 5 DAYS
MEAN BREATH CONCENTRATION AFTER FLUCTUATING VAPOR EXPOSURE, 2 MALES, 2 DAYS
MEAN BREATH CONCENTRATION AFTER NON-FLUCTUATING VAPOR EXPOSURE, 4 FEMALES, 5 DAYS
Breath Toluene Concentration, ppm
100
6
4
2
10
6
4
2
1
6
4
2
0.1
0
5
10
15
Time in Hours After Exposure

APPENDIX I

STATEMENT OF VOLUNTARY CONSENT

FOR RESEARCH INVESTIGATION OF

HUMAN EXPOSURE TO:

TOLUENE

I, _____, hereby agree to participate as a subject, in a program of research investigation under the direction and supervision of Dr. R. D. Stewart.

The general purpose of this research is to determine rates of uptake, excretion and metabolism of _____.

The studies have been described to me and the known risks involved in this experimental procedure have been explained to me. I understand that the most frequently described known risks are: none known at this level of exposure

I understand also that it is not possible to identify all potential risks in experimental procedures which involve controlled exposures to the chemical in a specially designed chamber.

I further understand that reasonable precautions and safeguards have been and will be taken to remove and reduce both the known and the potential but unknown risks and to provide for my safety and comfort.

I also understand that, while the program will be under the direction and supervision of Dr. R. D. Stewart, other professional persons who work with him may be designated to assist him or to act for him.

In view of those considerations, I hereby authorize Dr. R. D. Stewart and his representatives to proceed with the investigation on the understanding that I may terminate my service as a subject in this research at any time I so desire. I also authorize Dr. R. D. Stewart to use any type of data, pictures, films etc. for use in any scientific report or publication.

I am offering my service freely, in consideration of similar actions on the part of other subjects involved in like voluntary efforts to improve our society through research.

Witness _____ Signed _____

Investigator Subject

Date _____

HISTORY

PART 1

NAME | DATE

P. M. H.

GENERAL HEALTH | WT.

ILLNESSES | OP | HOSP. | INJ.

S.F

R.F.

D. MELL

T.B.C.

TYPHOID

MALARIA

NER. BK.

GOUT

MEDICATION

P. H.

RELIG. | ED.

VOCAT.

MARITAL

HABITS | SLEEP | COFFEE | CIG. | ALCOL.

WK. HRS./WK.

IMMUNIZATIONS

SMALLPOX

TETANUS

DIPTH.

POLIO

INFLU.

TYPH.

MEAS.

F. H.

M | W/H

F

MM

MF

FM

FF

D. MELL

LARGE INFANTS

STILLBORN

TBC

B.P.

HEART

COR. THROM

ANGINA

STROKE

BLEED. TEND

CA

ASTHMA

HAY FEVER

EPILEPSY

NER. BK.

INSANITY

GOUT

KIDNEY

PHYSICAL EXAMINATION

X = NOT EXAMINED - = NO; NEGATIVE
✓ = NORMAL; YES O = ABSENT

NAME | DATE

TEMP. | B.P. | P. | HT. | WT. | ST. WT.

APPEARANCE | POSTURE

HAIR — COLOR | TEXTURE | DISTRIBUTION

SCALP — CLEAN | ERUPTION | ALOPECIA

SKULL — DEFORMITIES | TENDERNESS

FACE — PALSIES | EXPRESSION | LIPS

EARS — CERUMEN | TYM MEMB | WATCH HEARD R L | TOPHI

NOSE — DISCHARGE | OBSTRUCTION | PERFORATION

MOUTH — BREATH | ULCERS | AB. PIGMENTATION

TEETH — R 8 7 6 5 4 3 2 1 | 1 2 3 4 5 6 7 8 L | X = CARIOUS, O = ABSENT
R 8 7 6 5 4 3 2 1 | 1 2 3 4 5 6 7 8 L | CLEAN | ADEQUATE CHEWING SURFACE

GUMS — RETRACTION | PYORRHEA

TONGUE — PROTRUDED MIDLINE | TREMOR | ATROPHY

TONSILS — STATUS | ENLARGED | INJECTION | EXUDATE

PHARYNX — GAG REFLEX | INJECTION | EXUDATE

EYES — COLOR | ARCUS SENILIS | PERRLA | NEOM | NYSTAGMUS
EXOPHTHAL | LID LAG | PTOSIS | PERIORBITAL EDEMA
VISION | NEAR R L | FAR R L | FIELDS
OPHTHAL | DISC | H GR. | A GR. | TONOMETER R L

LARYNX — VOICE NORMAL | MIDLINE | TUG

NECK — STIFFNESS | NODES | VEINS | CAROTID | TRACHEA | PALPABLE THYROID

SPINE — TENDERNESS | RIGIDITY | AB. CURVATURE

THORAX — SYMMETRICAL | CVA TENDERNESS | STERNAL TENDERNESS

RESPIRA — RATE | REGULAR | DEPTH | SYMMETRICAL | FORCED

LUNGS — COUGH | SPUTUM | PERCUSSION
RESONANT | BREATH SOUNDS | VESICULAR
RALES | TACTILE FREMITUS | VOICE SOUNDS

HEART — HEAVE | SHOCK | THRILL
APEX IMPULSE PALPABLE IN _____ I.C.S. _____ CM. TO L. OF M.C.L. FROM M.S.L. | B.C.D. EXTENDS _____ CM. TO L. OF M.S.L. _____ I.C.S.
SOUNDS A_2 P_2 M_1 M_2 | RHYTHM | MURMUR

BREASTS — SIZE NORMAL | TENDERNESS | MASSES

ABDOMEN — SYMMETRICAL | DILATED VEINS | ASCITES
PALPABLE LIVER | SPLEEN | KIDNEY | MASSES
TENDERNESS | RIGIDITY | SOUNDS | HERNIA

GENIT-ALIA — DISCHARGE | SKIN LESION | TESTES
PELVIC

ARMS — RADIAL PULSE | TREMOR | CLUBBING | CYANOSIS | JOINTS

LEGS — DORSALIS PEDIS | VARICOSITIES | EDEMA | ULCER
JOINTS

EYES	VISION	PAIN	GLASSES	
EARS	HEARING	DISCHARGE	PAIN	TINNITUS
NOSE	SMELL	OBST.	EPIS	DISCH.
C.R.	URI/YR	SORE THROATS	HORSENESS	COUGH
	SPUTUM	HEMOP	NIGHT SWEATS	FEVER
	WHEEZE	PAIN	DOE	
	EPEMA	OTHOP	PND	↑ B.P
G.I.	MOUTH			
	APPETITE	DIET	DYSPHAGIA	
	N & V	PAIN		
	STOOLS			
	JAUNDICE	MASS		
G.U.	FREQ.	NOC	PAIN	DYSURIA
	INCONTIN.	COLOR		
	ALB.	SUGAR	WBC	RBC
	V. D.			
M.S.	PREV. TRAUMA			
	NECK	BACK	VAR. VEIN	
	JOINTS	LEG CRAMPS		
NEURO	HEADACHE	TRAUMA		
	ATAXIA	PARALYSIS		
	ANESTH-PARE	TREMOR		
	FAINTING	CONVUL.		
	MEMORY	PERSONALITY		
SKIN	ERUPTION			
	ITCHING	COLOR CHANGE		
LYMPH-HEMAT.	BLEEDING DISORDER			
END.				
ALLERGY				
MENSES	ONSET	LAST WEEKS AGO	DURATION	FREQUENCY / PAIN
	MENOPAUSE	SPOTTING		
	V.D.	VAGINAL DISCHARGE		
BREASTS				