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Quantitative Assessment of the Effects of Postnatal Lead Exposure on the Habituation of Motor Activity in Rats

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I. Introduction

A. Lead (Pb)

1. History, Prevalence and Occurrence

Lead use dates back for centuries. In ancient civilizations it was used as a source of silver and also for statues, amulets, dishes, pigments, building work, sling shots, weights, and coins (Cory-Slechta, 1984). More recent analysis of lead deposition indicates that global emissions of lead have increased 2000-fold since early civilization with the greatest increase beginning in the 1920's when lead began to be used as an additive to gasoline (Schlag, 1987).

Lead's toxicity has been recognized for centuries. However, warnings about its neurotoxic effects have often been historically ignored. Lead is a naturally occurring element that is prevalent in virtually every level of the biosphere. Lead is a soft, heavy, gray-white metal that is relatively inert, has a low melting point, is a poor conductor of electricity and occurs naturally in four stable isotopes (Schlag, 1987). In addition to naturally occurring lead (e.g., from volcanic eruptions), human activities contribute a substantial amount to lead emissions. Schlag (1987) reported that an estimated 450,000 metric tons per year of lead emissions resulted from human activities, with almost 90% of the anthropogenic lead emissions in the atmosphere in the U.S. coming from the combustion of gasoline. Schlag (1987) also sites lead smelting, combustion of coal, and combustion of waste oil as generating the highest emissions of lead from stationary sources. Because of its prevalence in the environment there are numerous potential

sources of exposure to lead involving varying durations and concentrations. These sources include but are not limited to air, dust, soil, food, drinking water, and ingestion of lead-based paint.

Despite the steady decrease in the use of lead in gasoline, the total production of lead in the U.S. has not changed significantly in the last 30 years (Schlag, 1987). However, there has been a considerable change in lead-use patterns. Schlag (1987) reports that the primary use of lead is for the manufacture of storage batteries (72%) and secondarily for gasoline (7%). However, in spite of the consistent volume in the total production of lead, Bogden et al. (1997) points out that the elimination of lead in gasoline in the 1970s, and reduced use of lead in other sources of exposure such as outdoor paint, printing inks, and solder tin cans used for food storage, has resulted in well-documented and substantial decreases in blood-lead concentrations of all age groups in the United States. Yet despite these efforts, some segments of the population, young children in particular, continue to be exposed to excessive levels of lead from paint chips, soil, and various other sources.

2. Human Exposure and Risk

Clearly, there are many factors that influence the intensity or level of human lead exposure and the risks experienced by an individual, including age, sex, season, hand-to-mouth behavior (pica), occupation, race, socioeconomic status, diet, and cultural practices. Acute lead toxicity associated with blood-lead levels of 120 µg/dl or greater in adults, or 80 µg/dl or greater in children, may cause death or irreversible brain damage including increased cerebrospinal fluid pressure, convulsions, memory loss, and acute encephalopathy (Manser, 1989). Long-term exposure to lower concentrations of lead can give rise to many adverse central nervous system (CNS) effects that are more difficult to detect. Over the years, lead has been found to cause adverse health effects at successively

lower levels of exposure (Davis et al., 1993), which is part of the reason it continues to be an important public health issue.

Consequently, the United States Environmental Protection Agency (EPA) has continued to revise downward the criteria for "acceptable" blood-lead concentrations to its current 10-µg/dl mark, which is a target level for regulatory development and enforcement/clean-up purposes (Davis et al., 1993). This criterion was reached after EPA concluded that blood-lead levels exceeding 50 µg/dl are associated with a five-point decline in IQ, levels of 30 to 50 µg/dl with a four-point decline, and levels of 15 to 30 µg/dl with a decline of perhaps one to two points (Bellinger and Needleman, 1992). Bellinger and Needleman (1992) report that IQ differences of this magnitude are often dismissed as unimportant. However, because of the sigmoid shape of a normal cumulative frequency distribution for IQ, a shift of four to seven points in the mean can represent a four-fold difference in the percentage of children in the extreme tails of the distribution (Bellinger and Needleman, 1992).

With the steady decrease in lead exposure, resulting from the phase-out of lead in gasoline, has come increased concern about other lead exposure pathways. Major areas of concern include contaminated air from smelter emissions, drinking water, food, lead-based paint, and household dust and soil contaminated by deteriorating paint (Davis et al., 1993). Schlag (1987) reports that lead-contaminated soil is an area of concern because lead is strongly retained in most soils, and once deposited, will likely remain there for an extended period of time unless removed by erosion. In addition, experiments on lead in soil and paint show that 2 to 6 times as much lead can be biologically extracted from soil than from paint i.e., 3 times more lead is bioavailable from lead in soil than in paint (Mielke and Reagan, 1998).

Lead-contaminated soil, water, and paint have been recognized as potential sources of lead exposure for decades, but their relative contributions to lead intake among children remains poorly defined. Some argue that lead-based paint is the primary concern as a potential source of poisoning in children. Lead-based paint can contain as much as 40% lead, and is prevalent in dilapidated and old peeling houses (Schlag 1987). Recent statistics indicate that approximately 42 million homes in the U.S. contain lead-based paint, with as many as 12 million children under the age of 7 and 400,000 fetuses potentially exposed (Davis 1993; Nordberg et al., 1991; Mielke and Reagan 1998). Approximately 1.2 million children have sufficient exposure to lead-based paint to raise their blood-lead levels above 12 μg/dl (Davis 1993, Nordberg et al., 1991). While abatement of lead-based paint is technically feasible, the number of dwellings contaminated and the direct costs to achieve remediation seem to be the greatest obstacles (Davis et al., 1993). In contrast, Mielke and Reagan (1998) argue that soil lead, resulting from leaded gasoline and pulverized lead-based paint, is at least or more important than lead-based paint as a pathway of human lead exposure. Their conclusion is based largely on the bioavailability of lead, i.e., the likelihood of the child ingesting a sufficient dose of lead from lead-based paint chips and the ability of the intestinal tract to absorb and retain lead. Approximately 50% of ingested dietary lead is absorbed by children less than 5 years of age given that human absorption and retention of lead is a function of both particle size and chemical species. Research has shown that a substantial amount of lead is reabsorbed by food or other substances already in the digestive system. This limits the availability of lead to membrane absorption sites. This supports their argument that a high-dose source of lead does not mean that source poses a greater risk. Efforts to deal with lead exposure and abatement are on-going because of the enormous population potentially affected, especially children.

In terms of human exposure, childhood exposure has received the most attention since children are more sensitive than adults to the neurological effects of lead. The increased susceptibility of the immature brain to lead is thought to be a consequence of the following factors: increased opportunity for exposure, increased absorption and retention, and increased vulnerability of the developing CNS (Silbergeld et al., 1993). Children's cognitive function has for the most part been assessed with standardized IQ tests and other scales of early mental development (Davis et al., 1990). Bellinger et al. (1989), in a prospective cohort study, determined that vulnerability to low-level prenatal and postnatal lead toxicity varied with the children's age at exposure, level of exposure and socioeconomic status. This study measured infants' performance at age 6, 12, 18 and 24 months (based on classifications by social class and blood-lead levels taken from the umbilical cord or at 6 months of age) on the Mental Development Index (MDI) of the Bayley Scales of Infant Development. They found that regardless of the exposure classification (lead levels at birth or 6 months of age), the dose-dependence between lead and MDI scores differed in the "upper" and "lower" social-class groups more during the second year of life than during the first. When blood lead level at 6 months, rather than at birth, was the basis for exposure classification, the decrease in MDI scores with increasing lead level was apparent only among infants in the lower social class group and only at exposures considered to be high. However, when umbilical cord blood lead levels were used as the basis of exposure classification, the mean MDI scores between 6 and 24 months decreased as cord blood lead increased, with infants in the upper social class group tending to score higher than those in the lower social class group at 18 and 24 months of age. In addition, the MDI scores of infants in the high lead exposure group (cord blood-lead levels exceeding 10 μg/dl) were indistinguishable in the two social classes. In this cohort study, infants from the most advantaged families displayed deficits only when cord blood lead levels exceeded 10 μg/dl and did not appear to show deficits at any postnatal exposures (6, 12, 18, 24 months). These findings suggest that lead exposure

guidelines designed to safeguard preschool children might not adequately protect the fetus, given that the prevalence of umbilical cord blood lead levels greater than 10 µg/dl approaches 25% in urban areas of developed countries. Consequently, these infants may be at risk of developmental impairment regardless of their socioeconomic standing.

Recently there has been a considerable amount of research on lead levels in the deciduous teeth of children. Lead content in teeth has received increasing amounts of attention because it appears to be dose-related, is an indicator of overall long-term exposure to lead (unlike blood), and provides an indication of the relative body burden of lead (Schlag 1987). The particular area of tooth that is analyzed must be carefully scrutinized, since differences in the area analyzed may underlie some of the differences in reported results (Silbergeld et al., 1993). Silbergeld et al. (1993) reported that circumpulpar dentine appears to be the most accurate area to analyze rather than whole-tooth lead or lead in enamel. Silbergeld et al. (1993) also noted that dentine accumulation of lead does not continue throughout life and the spontaneous availability of teeth is limited to children, who obtain their adult teeth by about 9 years of age. Needleman et al. (1979) used tooth lead levels to classify asymptomatic 1st and 2nd grade children, and after controlling for confounders reported that high lead in the teeth was associated with decreased IQ, impaired attention and impaired speech performance. In addition, Needleman et al. (1990) reported in an 11-year follow-up study that associations found between lead and children's academic progress and cognitive functioning persisted into young adulthood, resulting in a seven-fold increase in failure to graduate from high school, lower class standing, greater absenteeism, impaired reading skills and deficits in vocabulary, fine-motor skills, reaction time and eye-hand coordination. These impairments in academic performance should not be taken lightly, given that three times as many children with an IQ of less than 80 will occur and only one-third as many with an IQ above 125 will occur as a result of a decrease in IQ of only 2 to 5 points (Manser, 1989).

3. Toxicokinetics

Accumulation of lead begins in utero and continues until age 50 to 60 years, followed by a decline in lead content due to such factors as dietary, metabolic and hormonal changes (Mushak, 1993). Lead is taken up in three kinetic compartments, with half-lives of 25 days in blood, 30 days in soft tissues (i.e., the kidney has the greatest uptake followed by the liver, heart, and brain) and up to several decades in bone, with bone containing >95% of the total body lead (Mushak, 1993; Nordberg et al., 1991; Rabinowitz, 1991; Silbergeld, 1991; and Schlag, 1987). Measurement of lead in blood is the most commonly used marker for lead exposure. However, these measurements mainly reflect recent lead exposure since the half-life of this compartment is only 25 days (Mushak, 1991; Silbergeld, 1991; and Schlag, 1987).

Following constant exposure, bone lead is in dynamic equilibrium with, and undergoes release to, blood (Mushak, 1991; and Schlag, 1987). The distribution and retention of lead in bone is complex. Bone accumulates lead and provides a marker of chronic exposure since its half-life is on the order of several decades (Mushak, 1993; Nordberg et al., 1991; Rabinowitz, 1991; Silbergeld, 1991; and Schlag, 1987). Recently, there have been several studies on bone lead as an indicator of chronic lead exposure and an internal source of lead exposure to the host organism (Nilsson et al., 1991; Nordberg et al., 1991; Pounds et al., 1991; and Rabinowitz, 1991).

Although bone is a major storage site for lead, it is not a physiological sink. Under conditions of either reduced exposure or bone demineralization, bone can become a significant internal source of lead exposure (Nordberg, 1991; and Silbergeld, 1991). Bone demineralization varies with age, nutritional and endocrine status, osteoporosis,

pregnancy, and lactation (Nordberg, 1991; Silbergeld, 1991; Silbergeld et al., 1988; and Weyermann and Brenner,1998). Silbergeld et al. (1988) examined the lead status of 2981 women before and after menopause using a NHANES II dataset compiled between 1976 and 1980. Their findings from post-menopausal women supported the hypothesis that physiological conditions which cause mobilization of bone calcium can also mobilize bone lead. In addition, the post-menopausal increase in lead levels was less in women with prior pregnancies. This observation supported the hypothesis that pregnancy also causes bone demineralization and lead release, resulting in less available lead in the post-menopausal period.

Evidence of bone-lead mobilization during pregnancy and lactation has been found in animals and humans. Keller and Doherty (1980) reported that lead transferred during lactation from adult female mice to their offspring greatly exceeded transfer during prenatal development. The rate of increase in lead retention, and soft-tissue lead concentrations, were also much greater in lactating females than in non-lactating females. In addition, relative lead retention (percentage of lead body burden $\pm$ SE) in the femurs of lactating females (3.9 $\pm$0.1%) exposed to lead prior to mating were reduced compared to non-lactating females (5.1 $\pm$0.1%). Manton (1985), in a 9-year study, measured the isotope ratios of lead in human blood from a married couple. During pregnancy the blood-lead level was attributed to mobilization of lead from bone, whose turnover rate would have increased to meet the calcium demands of late pregnancy. All of the aforementioned results support the fact that lactation results in relatively large calcium demands on the lactating mother, providing further evidence that lead sequestered in maternal bone is mobilized during lactation and subsequently transferred via milk to suckling offspring.

Mobilization of lead from bone during pregnancy has substantial toxicological significance given the adverse effects of lead on reproduction and cognitive development in young children. Nordberg (1991) reported that at low doses skeletal mobilization of lead can produce decreases in physical stature, as well as behavioral and cognitive deficits in infants. The assumption that blood-lead levels, which are usually measured only once at delivery, accurately reflect exposure of the mother and fetus throughout pregnancy may be one problem in the interpretation of many of these studies (Silbergeld, 1991).

B. Motor Activity as a Measure of Behavioral Neurotoxicity

Locomotor activity can be thought of as movement from place to place and is comprised of horizontally-directed and vertically-directed activity (Reiter & MacPhail, 1982). This process occurs naturally as animals explore their environment and appears to be sensitive to the effects of a vast array of chemicals. In the rodent, motor activity is a complex behavior consisting of a variety of motor acts, such as sniffing, grooming, rearing, and ambulation. Alterations in the frequency of this behavior could reflect toxicant-induced changes in any one or more sensorimotor functions, arousal, or motivational states (Tilson, 1987). The assessment of motor activity in rodents is one of the most common and fundamental behavioral tests used by neurobehavioral scientists. Consequently, it has been used extensively in behavioral toxicology and pharmacology, as both a measure of motor dysfunction and an apical test for screening purposes (Tilson, 1987).

For the purposes of this experiment a photocell device was used to assess motor activity. An activity count was registered each time a light beam was interrupted by the movement of an animal (Cory-Slechta, 1989). This apparatus was selected because it is relatively trouble-free in operation, can function independently of ambient illumination, provides no feedback to the animal and is indicative of the animals' ability to habituate. Habituation is

one of the most simple forms of learning (Platel and Porsolt, 1982). It refers to the observation of a diminished behavioral response with repeated exposure to a stimulus or test environment. With repeated exposure to a test environment, habituation is characterized by decreases in activity level across test sessions. That is, the activity level is highest at the beginning of testing, and thereafter decreases to a stable level. In this experiment, habituation of motor activity in rats was investigated as an experimental model of learning and memory processes. We defined learning as the decrease in activity observed when rats were exposed repeatedly to the same test environment (i.e., the photocell activity chamber). A decrease in activity upon repeated exposure (i.e., habituation) indicates that the animal remembered having been in that environment (Platel and Porsolt, 1982). Learning, therefore, can be described as change in behavior, while memory can be described as the preservation of that change in behavior. Learning in lead-exposed rats was studied in this experiment relative to that obtained in control rats.

The length of time activity is recorded may have a substantial effect on the interpretation of data. The guidelines for motor activity testing established by the U.S. EPA provide that "the test session shall be long enough for motor activity to approach asymptotic levels by the last 20 percent of the test session for most treatments and animals' activity counts shall be collected in equal time periods of no greater than 10 minutes duration" (Federal Register, 1985, p.12891). In this experiment motor activity levels decreased to a stable asymptotic level within 30 minutes; measurement of motor activity over this time period will be referred to as within-session habituation.

Habituation is also evident across test sessions (days) and is referred to as between-session habituation. To date there is very little research on between-session habituation. However, as early as 1978 Driscoll and Stegner recognized the importance of repeatedly recording activity across sessions. In this experiment, 30-day-old rats were exposed to

one of two concentrations of lead acetate solution and were tested for three daily 5-minute sessions. The number of open field squares that an animal entered during each minute of the test was recorded. Animals exposed to a low lead acetate solution (10^{-4}M) showed changes in overall activity (between-session) while animals exposed to the high lead acetate solution (10^{-2}M) showed changes in their relative rate of activity with high lead animals exhibiting a slower reduction in activity over time than did control or low lead animals. These differences in the differential rate of change may have been masked if only within-session habituation was studied. In addition, Platel and Porsolt, (1982) used photocell activity cages to investigate the ability of mice to habituate. They hypothesized that if habituation was a form of learning, it should be subject to forgetting. To test this hypothesis, 40 animals were given an acquisition session immediately followed by an IP injection of saline and then tested for retention 1, 3, 5 or 7 days later. They found that there was a marked decrease in activity when the two sessions were separated by a day, and that this activity decrement declined with increasing inter-session intervals, suggesting that forgetting occurred over time.

Several studies have reported increases in the motor activity of lead-exposed rats during early development. In addition, it has been suggested that this phenomenon provides an animal model of lead-produced hyperactivity in children (Driscoll and Stegner, 1978). There are, however, a number of contrasting findings on this subject. The primary reasons for the lack of consistency in these findings appear to be differences in (1) sample size, (2) techniques used to record activity, (3) effects of lead on body weight, (4) methods of administration and dosage levels of lead and (5) length and detail of activity recorded (Driscoll and Stegner, 1978; Rafales et al., 1978).

C. MK-801

The compound (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene-5,10-imine (MK-801) is an anticonvulsant which is formulated as the maleate salt. MK-801 is a white, non-hygroscopic, crystalline solid with good stability characteristics in ambient conditions and in weakly acidic and basic solutions. It has a molecular weight of 337.48. It is readily soluble in distilled water, methanol and dimethylacetamide, but only marginally soluble in acetone, acetonitrile and chloroform.

MK-801 is a selective, noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist. It does not interact directly with NMDA receptors but rather with phencyclidine (PCP) receptors which are coupled to the NMDA receptor ion channel (Wozniak et al., 1989). The region of the brain with the highest density of binding sites for MK-801 is the hippocampus, an area also enriched in NMDA receptors. These receptors are the main site of long-term potentiation (Butelman, 1988; Cohn et al., 1987) which is believed to be involved in learning and memory formation, thus leading to proposals that MK-801 produces performance deficits on learning and memory tasks. MK-801 is known for its potent "antineurodegenerative", anti-ischemic and anticonvulsant properties which seem to be linked to its efficacy as an NMDA antagonist (Butelman 1988, and Kant et al., 1991). In addition, it can reduce or block seizure activity and reduce the severity of behavioral impairment and neuronal cell loss from damage produced by centrally administered NMDA (McLamb et al., 1990).

Despite the potential beneficial effects of this NMDA antagonist, there have been reports of adverse neurobehavioral effects of this drug. MK-801 has been shown to impair learning of passive avoidance, acquisition of radial-arm maze performance and spatial acquisition in a water maze. In addition, several reports have investigated the effects of

NMDA and MK-801 on lead and/or motor activity (Cohn et al., 1994; Cohn et al., 1992; Guilarte and Whishaw, 1989).

Cohn et al. (1993) reported that lead-exposed rats developed a subsensitivity to the accuracy-impairing and rate-altering effects of MK-801 when tested on a multiple schedule of repeated learning and performance. The present study was therefore also designed to see if a similar subsensitivity could be obtained on the motor activity of lead-exposed rats. It was expected that the MK-801 dose-effect curves of the control rats would be elevated relative to lead-exposed rats if a differential behavioral sensitivity was produced by lead.

II. Materials and Methods

A. Animals and Husbandry. Male Long Evans rats served as subjects in all of the experiments (Table 1). They were housed in polycarbonate cages containing heat-treated pine bedding (Northeast Product Corporation, Warrington, NY) and were maintained on a 12-hour light/12-hour dark cycle. The room temperature was maintained at 72±2°C and 50%±10% relative humidity. The rats had unrestricted access to food (Purina Lab Chow 5001) and water (H_2SO_4 or a solution of 0.2% lead acetate dissolved in deionized water).

B. Apparatus. Groups of adult male Long-Evans rats were transported in individual plastic cages from the colony room to the laboratory where they were tested. Motor activity was recorded in six activity chambers (Motron Electronic Motility Meters, Motron Produkter, Stockholm, Sweden). Each consisted of a Plexiglas chamber (33 x 21 x 26 cm) with a removable lid containing holes for ventilation. The Plexiglas chamber was placed on top of a platform containing a matrix of 40 photodetectors

illuminated by a single overhead incandescent lamp (GE 30R20, 30 W). 8 rearing photodetectors were located on each side of the chamber approximately 10 cm above the platform. Each horizontal and vertical movement of a rat interrupting a photobeam was recorded as an activity count. The apparatus was placed in a wooden enclosure lined with acoustically absorbent rubber (FM11m /Southern Kinetics, Raleigh, NC) and containing a fan (Rotron No. WR2A1, Woodstock, NY) that provided continuous ventilation. The six chambers were located in a small test room lined with acoustical tile. Data collection was carried out with a microprocessor located in an adjacent room. Proper operation of the photodetectors and the data-collection program were checked daily by turning the overhead lamp on and off and manually testing the rearing photodetectors.

C. **Study Design.** Motor activity of individual animals was measured during 30-minute sessions that were signaled by illumination of the overhead incandescent lamp. Motor activity (both horizontal and vertical activity) for each rat was recorded in five 6-minute intervals during the 30-minute session. All testing was done between 1000 and 1700 hours.

D. Chemicals. Exposed rats in all experiments were given unrestricted access to 0.2% lead acetate (Fisher Scientific) dissolved in their drinking water while control rats received unrestricted access to deionized water. In one experiment, rats were also injected subcutaneously (s.c.) with either physiological saline or with 0.03, 0.1, 0.3 or 1 mg/kg of MK-801 maleate (Research Biochemicals Inc., Natick MA) dissolved in physiological saline. The 0.1-mg/kg dose was given twice to each rat to ensure reproducibility of effects. Injections were administered twice a week (Tuesdays and Fridays) over four weeks, with Thursdays' data representing non-injected control values.

E. Statistical Analysis. All data sets were entered into computer files and summary data were compiled using RS1. Quantitative analyses were undertaken of habituation within test sessions, as well as between test sessions, in control rats and in rats exposed postnatally to lead in drinking water. Additional analyses were carried out on data sets which were assembled from historical records of a number of rats that had been used as controls in previous unrelated research. Habituation measures included the habituation ratio, half-life, and the Index of Curvature (IOC). The habituation ratio expresses the level of activity at the end of testing as a ratio of the activity level at the beginning of testing. The half-life measure is the time (in minutes or sessions) at which one-half of the total activity occurred. The IOC statistic utilizes the distribution of activity across intervals (five 6-minute intervals within a session or five complete testing sessions) to calculate deviations from a theoretical line of no habituation (IOC=0). Coefficients of variation [CV=(standard deviation/mean) x 100%] were also calculated to represent between-subject variability. Habituation measures were evaluated on the basis of data requirements, stability and sensitivity to the effects of lead. Because of the relatively large number of data sets available (three replicates of the effect of lead plus controls, as well as 54 historical control values), distributions were created for each of the habituation measures, from which estimates of the risk of reduced habituation due to lead exposure could be calculated.

In order to quantitatively estimate the risk of reduced habituation due to lead exposure, distributions of habituation measures were established for lead-exposed rats, for concurrent-control rats and for historical-control rats. Distributions for the control rats were then transformed to z-scores. The means of the distributions for lead-exposed rats were also expressed as z-scores. An arbitrary criterion of $z=1.65$ or $z=1.25$ was then set for the control rats for reduced habituation. Using this criterion an estimated 5% or 10%, respectively, of the control rats would be expected to show reduced habituation. The

same criterion for reduced habituation was applied to the distribution of values for the lead-treated rats, after adjustment for displacement of the distribution relative to that of control rats. The corresponding frequency of lead-treated rats showing reduced habituation was then estimated from the z-scores and the ratio of estimated occurrence of reduced habituation for lead-treated rats relative to control rats was finally calculated. Quantitative estimates of the risk of reduced habituation following lead exposure were compared when based on concurrent-control rats as well as when based on historical-control rats.

The above analysis of estimated risk was based on theoretical areas under the curve of the z-score distribution. A final analysis used a relative-risk analysis (Hennekens and Buring, 1987). For this analysis, a 2x2 contingency table was created based on lead exposure and whether reduced habituation was or was not obtained, as shown below in Figure 1.

		Reduced habituation	
		+	-
Lead	+	**a**	**b**
Exposure	-	**c**	**d**

Figure 1. Representation of a 2x2 contingency table from a case-control or cohort study.

The relative-risk ratio (RR) was then calculated by the formula:

$$RR = \frac{a/(a+b)}{c/(c+d)} = \frac{\text{Incidence in the exposed group}}{\text{Incidence in the control group}}$$

III. Results

Motor activity assessments of day 1 versus day 5 are compiled in Table 2. In general the level of activity (horizontal and vertical) on day 1 is higher for control rats than lead rats with the exception of horizontal activity for the lead-exposed rats in experiment 130. Mean activity levels of lead-exposed rats from the three experiments, expressed as a percentage of the levels of control rats on day 1, were 88%, 76% and 113% for horizontal activity and 80%, 70% and 98% for vertical activity. In contrast, the activity levels of lead-treated rats (expressed as a percentage of the levels of control rats) on day 5 resulted in reliable increases of 129%, 126% and 123% for horizontal activity and 124%, 132% and 123% for vertical activity in the three experiments, respectively.

A. BETWEEN-SESSION HABITUATION

Figures 2, 3, and 4 illustrate between-session activity changes for the three experiments (i.e., horizontal and vertical activity counts collected in 30-minute sessions over 5 days for experiments 105, 122, and 130, respectively). A decrease in the level of activity across the 5-day period was evident in all the experiments with the exception of the horizontal activity for the lead group in experiment 122, which demonstrated a 27% increase in activity from a mean of 2635 total counts on day 1 to 3338 counts on day 5.

1. Habituation Ratio. The concurrent-control rats had a mean habituation ratio of approximately 0.71 (Table 3). This ratio was equivalent to a 29% reduction in activity level across the 5 days of testing. The lead rats, in contrast, showed no signs of

habituation and instead their mean habituation ratio increased to 1.03. There was a statistically significant difference in the means for the horizontal habituation ratio between concurrent-control rats and lead rats ($p<0.02$). In addition, the coefficient of variation for lead rats (66.6%) was twice that of the concurrent-control rats (25.4%). This high level of variability demonstrated by the lead rats may explain (1) the marked difference between their mean (1.03) and median (0.82) habituation ratios and (2) the frequency distributions being skewed or shifted to the right. The same trends were noted for vertical activity.

These results indicate that over 5 days of testing concurrent-control rats demonstrated a 29% reduction in activity (i.e., habituation) while lead rats showed no signs of habituation.

2. Half-life. The half-life for activity over time was significantly different ($p\leq0.01$) between concurrent-control rats (2.21 sessions) and lead rats (2.49 sessions). This result indicates that concurrent-control rats emitted one-half of their total activity in a shorter period of time than did the lead-exposed rats.

3. Index of Curvature. There was a marked difference ($p\leq0.02$) in mean index of curvature between concurrent-control rats (-0.07) and lead rats (0.00). The mean index of curvature value for lead rats approached zero, which indicates little or no habituation took place.

B. WITHIN-SESSION HABITUATION

Figures 5, 6, 7, 8 and 9 illustrate within-session activity for experiment 105 (i.e., horizontal and vertical counts collected in five 6-minute intervals in each of 5 sessions). Examination of horizontal activity (on day 1) reveals that activity for control rats (N=12) at the beginning of the test session was elevated relative to that for lead rats (N=12). However, by the end of testing, activity levels for control rats were below those of the lead rats. Day 2 activity for the two treatment groups was about equal. Finally, on days 3, 4 and 5, activity levels for lead rats were elevated relative to control rats. The same trends were obtained for vertical activity. These data indicate that control rats showed more habituation than did the lead rats.

Figures 10, 11, 12, 13 and 14 illustrate within-session activity for experiment 122. The activity levels in this experiment were not as consistent as those found in experiment 105. Examination of horizontal activity on days 1 and 2 reveals that activity for control rats (N=9) at the beginning of the test sessions were elevated relative to lead rats (N=8). However, by the end of testing, activity levels for control rats were below those of lead rats. On day 3 activity levels for control rats were slightly elevated relative to lead rats. Finally on days 4 and 5 activity levels of the lead rats were elevated relative to those of control rats. The same trends were demonstrated for vertical activity with the exception of day 3. On day 3, vertical activity levels for lead rats was slightly elevated relative to control rats within the 30-minute test session. However, the change in activity over time was similar for the two groups.

Figures 15, 16, 17, 18 and 19 illustrate within-session activity for experiment 130. Horizontal activity levels for lead rats (N=12) was elevated relative to control rats (N=12) throughout each test session and across sessions. Both groups showed signs of

habituation but more habituation was evident in the control rats relative to the lead rats. Vertical activity levels, on the other hand, were not as consistent across test sessions. On day 1, vertical activity for control rats at the beginning of the test session was elevated relative to that for lead rats. However, by the end of testing, activity levels for control rats were below those of the lead rats. Activity levels for both treatment groups were about equal on day 2, 3, 4 and 5. These data indicate similar vertical habituation patterns over time for both treatment groups.

1. Habituation Ratio. Examination of activity levels at the end of a test session compared to the levels at the beginning revealed that, within their respective treatment groups, concurrent-control rats demonstrated more habituation on day 1 through day 5, with horizontal habituation ratios of 0.26, 0.31, 0.35, 0.32 and 0.30 (Tables 4 and 5). Lead rats, on the other hand, demonstrated less habituation in horizontal activity, with habituation ratios of 0.51, 0.37, 0.36, 0.45, and 0.45. The same trends were demonstrated for vertical activity. Since greater habituation is reflected by smaller ratios, these results indicate that during each daily 30-minute test session concurrent-control rats demonstrated greater habituation than did lead rats.

2. Half-life. Examination of the time course of habituation for horizontal activity revealed that throughout each test session the overall half-life measures for lead rats were higher, as evidenced by half-life measures of 1.93, 1.64, 1.62, 1.62 and 1.70 sessions. Concurrent-control rats, on the other hand, had half-life measures of 1.57, 1.65, 1.61, 1.60 and 1.59. These results indicate that lead rats took longer to habituate than did control rats.

3. Index of Curvature. Comparison of Tables 3 and 4 indicate that there was a marked difference between concurrent-control rats and lead rats. Index-of-curvature values for

concurrent-control rats were more negative over the five days of testing with IOC values of –0.28, -0.26, -0.35, -0.40 and –0.38. Hence, lead rats had Index-of-Curvature values more closely approaching zero, with IOC values of –0.16, -0.22, -0.24, -0.18 and –0.23, indicating less habituation than in the concurrent-control rats. The same trends were demonstrated for vertical activity.

C. MK-801 Effects on Motor Activity

The structure of this compound is illustrated in Figure 20. Figures 21, 22 and 23, illustrate the effects of MK-801 on motor activity. Motor activity increased with dose up to a maximum at 0.3 mg/kg, and then decreased toward control values at the highest dose. No differences in the effects of MK-801 on motor activity were found between control and lead-treated rats.

D. QUANTITATIVE RISK ASSESSMENT

Tables 8, 9 and 10 list the between-session habituation measures for concurrent-control rats (N=32), lead rats (N=32) and historical-control rats (N=54), respectively. The results of the relative risk analysis for lead rats based on reduced habituation in an estimated 5% (tables 15 and 17) and 10% (tables 16 and 18) of control rats (i.e., both concurrent-control and historical-control rats) are shown in tables 15 through 18. Three key areas of comparison were relative risk based on 1) reduced habituation in an estimated 5% vs. 10% of the control rats, 2) reduced habituation in lead rats when compared to concurrent-control vs. historical-control rats, and 3) reduced habituation in control rats calculated from actual habituation measures vs. habituation measures based on z-scores analysis.

Comparison of the relative risk of reduced habituation for lead rats, when based on 5% of the control rat population versus when based on 10%, revealed that the risk of failing to habituate was greater when based on the more stringent 5% criterion. Relative risk (if placed in ascending order) for lead rats based on 5% of the control population ranged from 1.4 to 25.2 while the relative risk for lead rats based on 10% of the control rat population ranged from 1 to 6.

Comparison of the relative risk for lead rats based on reduced habituation in concurrent-control rats with that based on historical-control rats revealed that the relative risk was always greater when based on concurrent-control rats.

Comparison of the relative risk for lead rats based on reduced habituation in an estimated 5% or 10% of control rats, calculated from actual habituation measures as opposed to those calculated from habituation measures converted to z-scores, revealed that the relative risk was higher when based on z-scores for 5% estimates.

IV. DISCUSSION

Although a variety of treatments and conditions have been shown to affect the within-session habituation of motor activity, very little research has focused to date on between-session habituation. In addition, there have been virtually no systematic comparisons of the two forms of habituation. Furthermore, while motor activity has been used to assess many neurotoxic substances, including the screening of chemicals for neurotoxic potential, very little research has been carried out on the habituation of motor activity as a measure of cognitive function. This study was designed to determine if the altered habituation demonstrated in rats postnatally exposed to lead in drinking water is reproducible. A quantitative comparison of between-session and within-session habituation was also undertaken to determine if there were differences in the two measures, which would cause a conservative or liberal risk assessment of lead exposure.

Despite, its elimination from gasoline, lead is still very prevalent in our society. It causes adverse health effects at very low levels. In addition, unlike exposure to other harmful pollutants, which may take place as the result of an accident or residence in a particular location, virtually all children in industrialized nations are chronically exposed to lead. Many of these children carry lead burdens that are disturbingly close to those at which health is compromised (Bellinger et al., 1992). Consequently, lead continues to be a vital public health issue. Therefore any efforts to identify the most sensitive indicators of lead effects are beneficial and warrant further discussion. In particular, this method of assessing lead effects should be the focus of future studies. A range of characteristics were used to determine lead effects and to compare between-session and within-session habituation: quantification of habituation ratio, half-life, index of curvature, relative risk ratio and support from related literature. Based on these qualitative and quantitative criteria the following effects of lead ingestion are evident. First, both lead and control

rats habituated over a five-day period (although in varying amounts). Second, exposure to lead increased overall activity relative to control rats. Finally, lead-exposure reduced the between-session and within-session habituation of motor activity.

The findings of this study demonstrate the importance of comparing between-session and within-session habituation. Examination of between-session activity illustrates the complexity of measurement when activity levels are changing at different rates for different experimental groups. Examination of figures 2, 3 and 4 reveal an increased mean number of between-session activity counts for lead rats relative to controls. In addition, lead rats displayed a slower reduction in activity over time than did control rats. These results are similar to those found by Driscoll and Stegner (1978) where they concluded that animals exposed to high lead acetate solution (10^{-2}M) showed changes in their relative rate of activity with high lead animals exhibiting a slower reduction in activity over time than did control or low lead animals..

Examination of within-session activity reveals an increased mean number of within-session activity counts for lead rats relative to controls in two of the three experiments, although these differences were not statistically significant. In addition, the change in activity over time for lead and control rats was similar. Moreover, examination of table 7 reveals that, using the methods of quantification applied in this study, there is more variability and therefore an increased likelihood of obtaining errors in calculating within-session habituation relative to between-session habituation. Nevertheless, quantification of within-session activity is essential to understanding the differential rates of change, which occur across days. Measurement of activity or habituation using only one of the aforementioned methods without comparison with others may limit interpretation of results.

Although the synergistic effects of MK-801 and lead have been studied, differences in motor activity have not been published. Therefore, an additional experiment was conducted in order to see if lead-exposed rats developed a subsensitivity to the activity-altering effects of MK-801.

Exposure to lead has been reported to inhibit MK-801 binding and to alter other NMDA receptor complex-associated functions (Cohn et al., 1993). Cohn et al., (1993) reported that acute administration of MK-801 (0.05-0.3 mg/kg, i.p.) resulted in decrements in accuracy in both repeated acquisition (RA) and performance (P) components of a multiple schedule of repeated learning, indicative of non-specific effects on behavior rather than specific effects on learning. Moreover, they found that lead attenuated all the effects produced by MK-801.

Although the results reported by Cohn et al. (1993) were the impetus for this study there were several crucial differences in the research methods used by our laboratory and theirs. For instance, test procedure (motor activity as opposed to a multiple operant schedule of repeated learning and performance), age at which exposure began (birth as opposed to weaning), and concentration of lead (1060 ppm as opposed to 50 and 250 ppm). In addition, for this study administration of MK-801 occurred after a steady state level of activity was achieved. That is, both treatment groups (concurrent-control and lead rats) had already habituated. Therefore the effects of MK-801 on habituation were not tested. All of the aforementioned differences may have contributed to the substantial overlap in motor-activity effects seen among concurrent-control and lead rats dosed with MK-801. In conclusion MK-801 produced equivalent changes in motor-activity whether lead was present or not.

In addition to determining lead effects on habituation, the experiment also assessed the quantitative risk estimation of the effect of lead on habituation. To ensure an acceptable level of homogeneity relative risk was compared based on: 1) reduced habituation in 5% vs. 10% of control rats, 2) reduced habituation in concurrent-control rats vs. historical-control rats and 3) reduced habituation in control rats calculated from actual habituation measures vs. habituation measures based on z-score distribution.

Relative-risk ratios were determined for lead rats based on an arbitrary criterion of z=1.65 (5%) or z=1.25 (10%) representing reduced habituation in 5 or 10% of the control (i.e., concurrent-control and historical-control) rat populations. Although the sample sizes in this experiment (lead N=32, concurrent-control N=32 and historical-control N=54) are relatively large for laboratory research they are small in comparison to traditional epidemiological studies. Possibly due to sample size, relative risk calculated based on reduced habituation in an estimated 5% of control rats did not always prove to be effective. In 3 out of 24 of the relative risk-ratios calculated at the 5% level, all of the control rats habituated. To adjust for this situation, relative-risk ratios were calculated based on 1 control rat failing to habituate. In addition, relative risks were calculated based on reduced habituation in an estimated 10% of the control rat population. Relative risks were higher when based on the more stringent criterion of 5%. This may be so because lead rats have frequency distributions which are skewed to the right while control rats have frequency distributions that are more normally distributed. Calculating relative risk at 10% may mask the effect of this skewed distribution and consequently underestimate relative risk.

Comparison of relative risk for lead rats based on reduced habituation in concurrent-control rats with that based on historical-control rats revealed that relative-risk values were higher when based on concurrent-control rats. Consequently estimates based on

historical-controls may underestimate risk. This is very important since comparisons of an exposed population with a concurrent-control population are the preferred method of comparison whether studying rat populations in the laboratory or human populations in epidemiological studies. Of course, it is possible that the selection of the particular historical-control database may have influenced the outcome of the risk comparison. Systematic comparisons such as these are vital to understanding the utility of historical-control data in estimating the risk of adverse effects of environmental pollutants.

Comparisons of relative risk calculated when based on actual habituation measures as opposed to transformed z-scores revealed that the relative-risk values were higher when based on z-scores. This was not the expected result. However, transforming actual habituation measures to z-scores was based on theoretical areas under the curve of the z distribution, which is normally distributed. This may not account for the skewed tail demonstrated in lead frequency distributions, which may cause the relative risks based on z-scores to overestimate the risks especially when based on the 5%.

All of the aforementioned results taken together, suggest that the relative risk for lead rats, when based on reduced habituation in an estimated 5% of concurrent-control rats and calculated from actual habituation measures, are the most appropriate means of quantifying the adverse effects of lead on habituation. From this perspective, lead rats are 10 times as likely as concurrent-control rats to show signs of reduced habituation based on the horizontal and vertical habituation ratios. They are 4.5 (horizontal) and 2.7 (vertical) times as likely to show signs of reduced habituation based on the half-life measure and 5.5 (horizontal) and 9 (vertical) times as likely based on the index of curvature.

The large risk ratios quantified in this study should not be taken lightly given the potential public health threat. Relative risk calculated based on traditional laboratory analyses may exhibit small effects in comparison to traditional epidemiological studies. However, when these effects are extrapolated to human populations they maybe of substantial significance for public health. For example, a small downward shift in IQ in an individual child may not be significant but when society as a whole is considered, such a shift may be of substantial significance, especially if millions of children are included and the effect persists into later life. This is a considerable dilemma that public health officials have not yet fully faced. Clearly the trend in public health policy is to move toward the goal of reducing blood lead levels. However, while progress has been substantial over the past two decades, much remains to be done.

Table 1. GENERAL TESTING INFORMATION

Experiment #	Sample Size	DOB	Dates of Testing	Age at Testing	Blood Lead Levels
105	12	Sep-92	1/25-1/29/93	120 days	55.8+9.1 µg/dl
122	9	Apr-93	7/12-7/16/93	90 days	60-80µg/dl
130	12	Jul-93	8/30-9/4/93	60 days	57.4+12.7 µg/dl

Table 2. MOTOR ACTIVITY ASSESSMENT RESULTS

	TREATMENT		Day 1	Day 5	Day 5/Day1
Experiment 105	CONTROL	HA[a]	4062±302	2697±178	.69±252
	(N=12)	VA[b]	249±30[c]	140±20	.59±.22
	LEAD	HA	3589±274	3492±289	1.02±.35
	(N=12)		(88%)[d]	(129%)	
		VA	199±25	173±22	.94±.46
			(80%)	(124%)	
Experiment 122	CONTROL	HA	3455±243	2645±233	.77±.03
	(N=9)	VA	161±26	88±15	.57±.04
	LEAD	HA	2635±526	3338±393	1.32±1.29
	(N=9)		(76%)	(126%)	
		VA	122±31	116±31	1.73±.55
			(70%)	(132%)	
Experiment 130	CONTROL	HA	4257±616	2851±429	.57±.21
	(N=12)	VA	323±47	147±26	.38±.25
	LEAD	HA	4808±279	3497±241	.74±.14
	(N=12)		(113%)	(123%)	
		VA	318±23	181±27	.57±.26
			(98%)	(123%)	

[a]HA: Horizontal activity

[b]VA: Vertical activity

[c]Values represent X±SEM total photocell interruptions.

[d]Values represent activity levels of lead-treated rats expressed as a percentage of the levels of control rats.

TABLE 3. BETWEEN SESSION

		Horizontal Difference	Vertical Difference	Horizontal Ratio	Vertical Ratio	Horizontal 1/2 Between	Vertical 1/2 Between	IOC Horizontal	IOC Vertical
CONTROL RATS N=33	MEAN	1294.94	135.22	0.71	0.54	2.21	2.04	-0.07	-0.12
	MEDIAN	1081.00	121.00	0.70	0.54	2.19	2.04	-0.07	-0.10
	ST. DEV.	859.05	92.66	0.18	0.20	0.28	0.35	0.05	0.08
	CoV	66.34	68.53	25.36	36.78	11.28	17.28	-72.65	-68.44
PB RATS N=33	MEAN	-502.97	64.16	1.03	1.05	2.49	2.30	0.00	-0.06
	MEDIAN	815.00	75.00	0.82	0.68	2.33	2.29	-0.04	-0.07
	ST. DEV.	5770.28	116.47	0.69	1.31	0.48	0.55	0.13	0.14
	CoV	1147.24	181.53	66.64	124.52	19.24	23.83	-3820.00	-246.80
HISTORICAL CONTROL RATS N=54	MEAN	922.41	88.02	0.80	0.68	2.32	2.16	-0.05	-0.10
	MEDIAN	1082.50	86.00	0.74	0.55	2.30	2.09	-0.06	-0.11
	ST. DEV.	1031.38	100.18	0.24	0.41	0.27	0.49	0.06	0.13
	CoV	111.81	113.82	30.17	60.38	11.68	22.90	-131.71	-128.95

Table 3. Between session habituation measures for concurrent control rats (N=32), Pb rats (N=32), and historical control rats (N=54).

TABLE 4. CONCURRENT CONTROL RATS

		Horizontal Difference	Vertical Difference	Horizontal Ratio	Vertical Ratio	Horizontal 1/2 Within	Vertical 1/2 Within	IOC Horizontal	IOC Vertical
DAY 1	MEAN	1036.64	106.00	0.26	0.15	1.57	0.78	-0.28	-0.43
	MEDIAN	1055.00	102.00	0.26	0.12	1.65	1.10	-0.25	-0.46
	ST. DEV	448.78	61.00	0.21	0.22	0.42	0.96	0.13	0.18
	CoV	43.29	57.55	80.16	142.91	26.44	121.99	-47.04	-40.84
DAY 2	MEAN	754.73	70.70	0.31	0.18	1.65	1.04	-0.26	-0.39
	MEDIAN	830.00	72.00	0.31	0.10	1.77	1.00	-0.23	-0.42
	ST. DEV	359.56	43.78	0.22	0.23	0.38	0.72	0.13	0.16
	CoV	47.64	61.92	69.92	127.39	23.16	69.58	-50.70	-40.65
DAY 3	MEAN	690.39	58.67	0.35	0.23	1.61	1.07	-0.35	-0.35
	MEDIAN	661.00	51.00	0.44	0.23	1.75	1.26	-0.34	-0.34
	ST. DEV	421.33	40.71	0.24	0.23	0.43	0.71	0.16	0.16
	CoV	61.03	69.39	68.69	104.09	26.39	66.22	-46.23	-46.23
DAY 4	MEAN	723.12	61.06	0.32	0.18	1.60	0.05	-0.40	-0.40
	MEDIAN	805.00	61.00	0.36	0.08	1.62	1.15	-0.39	-0.39
	ST. DEV	350.28	37.76	0.24	0.26	0.35	2.21	0.19	0.19
	CoV	48.44	61.84	74.66	141.80	21.68	4473.68	-46.50	-46.50
DAY 5	MEAN	709.45	48.91	0.30	0.19	1.59	0.67	-0.38	-0.38
	MEDIAN	735.00	46.00	0.32	0.08	1.58	1.13	-0.39	-0.39
	ST. DEV	344.98	29.94	0.25	0.28	0.45	1.91	0.17	0.17
	CoV	48.63	61.21	81.02	148.25	27.97	284.23	-45.33	-45.33

Table 4. Within session habituation measures for concurrent control rats (N=32) collected in five 6-minute intervals in five days of testing.

TABLE 5. Pb RATS

		Horizontal Difference	Vertical Difference	Horizontal Ratio	Vertical Ratio	Horizontal 1/2 Within	Vertical 1/2 Within	IOC Horizontal	IOC Vertical
DAY 1	MEAN	652.94	58.12	0.51	0.48	1.93	1.66	-0.16	-0.23
	MEDIAN	645.00	55.00	0.51	0.44	1.92	1.67	-0.13	-0.20
	ST. DEV	455.04	51.84	0.32	0.44	0.58	1.01	0.14	0.21
	CoV	69.69	89.19	62.72	90.67	29.92	60.44	-83.45	-94.47
DAY 2	MEAN	769.73	62.30	0.37	0.28	1.64	1.08	-0.22	-0.30
	MEDIAN	832.00	58.00	0.38	0.32	1.69	1.34	-0.20	-0.27
	ST. DEV	352.04	36.37	0.24	0.25	0.65	1.06	0.13	0.18
	CoV	45.74	58.38	64.69	91.25	39.91	98.09	-62.03	-59.61
DAY 3	MEAN	732.24	68.79	0.36	0.29	1.62	0.54	-0.24	-0.34
	MEDIAN	697.00	58.00	0.42	0.29	1.76	1.20	-0.18	-0.30
	ST. DEV	393.86	45.94	0.23	0.23	0.49	2.87	0.15	0.20
	CoV	53.79	66.78	62.77	81.08	30.12	526.41	-60.83	-59.74
DAY 4	MEAN	619.18	48.74	0.45	0.30	1.62	1.46	-0.18	-0.29
	MEDIAN	619.00	46.00	0.47	0.22	1.89	1.59	-0.16	-0.26
	ST. DEV	318.92	31.92	0.21	0.28	1.35	0.70	0.10	0.19
	CoV	51.50	65.63	46.50	91.73	83.02	48.25	-58.31	-65.52
DAY 5	MEAN	604.18	56.50	0.45	0.24	1.70	1.01	-0.23	-0.38
	MEDIAN	811.00	57.00	0.31	0.18	1.60	1.15	-0.24	-0.37
	ST. DEV	1013.60	36.53	0.80	3334.00	0.69	1.10	0.17	0.21
	CoV	167.76	64.65	177.90	138.22	40.66	108.64	-73.91	-55.60

Table 5. Within session habituation measures for Pb rats (N=32) collected in five days of testing.

TABLE 6. HISTORICAL CONTROL RATS

		Horizontal Difference	Vertical Difference	Horizontal Ratio	Vertical Ratio	Horizontal 1/2 Within	Vertical 1/2 Within	IOC Horizontal	IOC Vertical
DAY 1	MEAN	830.37	78.52	0.35	0.19	1.73	1.25	-0.21	-0.33
	MEDIAN	866.50	80.00	0.35	0.17	1.75	1.28	-0.21	-0.32
	ST. DEV.	217.32	23.73	0.16	0.14	0.21	0.39	0.07	0.10
	CoV	26.17	30.22	45.93	73.60	12.00	30.80	-32.00	-31.10
DAY 2	MEAN	690.50	54.93	0.41	0.31	1.76	1.31	-0.20	-0.30
	MEDIAN	754.00	56.00	0.40	0.18	1.78	1.31	-0.18	-0.30
	ST. DEV.	250.19	29.77	0.17	0.38	0.25	0.67	0.08	-0.16
	CoV	36.20	54.20	42.20	121.70	14.30	51.60	-42.40	-53.10
DAY 3	MEAN	654.72	46.33	0.43	0.33	1.74	1.26	-0.19	-0.28
	MEDIAN	630.00	41.50	0.45	0.31	1.76	1.34	-0.35	-0.28
	ST. DEV.	254.17	25.53	0.18	0.26	0.23	0.53	0.07	0.12
	CoV	38.80	55.10	41.90	77.60	13.10	42.30	-38.00	-44.50
DAY 4	MEAN	52.39	43.50	0.45	0.48	1.77	1.41	-0.19	-0.26
	MEDIAN	647.00	39.50	0.43	0.25	1.78	1.29	-0.17	-0.26
	ST. DEV.	293.82	33.23	0.25	0.93	0.33	0.87	0.10	0.19
	CoV	45.00	76.40	54.90	173.40	18.90	61.80	-51.10	-72.60
DAY 5	MEAN	673.30	43.46	0.39	0.27	1.69	1.30	-0.21	-0.31
	MEDIAN	687.50	41.50	0.37	0.17	10.64	1.35	-0.20	-0.31
	ST. DEV.	230.61	23.10	0.19	0.26	0.39	0.69	0.10	0.17
	CoV	34.30	53.20	49.40	98.10	22.90	53.00	-47.96	-54.97

Table 6. Within session habituation measures for historical control rats (N=54) collected in five days of testing.

Table 7. Exclusions

Historical Control Rats
6 Experiments: N=54

	270 Observations Within-session	54 Observations Between-session
Difference Score	0	0
Habituation Ratio	VA=35 (13%)	0
Half-life	VA=4 (1.5%)	0
IOC	0	HA=15 (12%) VA=12 (22%)

Concurrent Controls
3 Experiments: N=32

	165 Observations Within-session	32 Observations Between-session
Difference Score	0	0
Habituation Ratio	HA=11 (7%) VA=19 (12%)	0
Half-life	HA=11 (7%) VA=14 (9%)	0 0
IOC	HA=11 (7%) VA=10 (6%)	HA=4 (12%) VA=3 (9%)

Pb Rats
3 Experiments:N=32

	165 Observations Within-session	32 Observations Between-session
Difference Score	0	0
Habituation Ratio	HA=7 (4%) VA=10 (6%)	0
Half-life	HA=7 (4%) VA=8 (5%)	0
IOC	HA=7 (4%) VA=5 (3%)	HA=12 (36%) VA=10 (30%)

Indicates that "1" was substituted for "0" if no activity occurred in the last testing interval.
Indicates that the majority of activity occurred during the first testing interval.
Indicates that the IOC was a positive number.

Table 7. Exclusions

Historical Control Rate
6 Experiments: N=54

	270 Observations Within-session	54 Observations Between-session
Difference Score	0	0
Habituation Ratio	VA=35 (13%)	0
Half-life	VA=4 (1.5%)	0
IOC	0	HA=15 (12%) VA=12 (22%)

Concurrent Controls
3 Experiments: N=32

	165 Observations Within-session	32 Observations Between-session
Difference Score	0	0
Habituation Ratio	HA=11 (7%) VA=19 (12%)	0
Half-life	HA=11 (7%) VA=14 (9%)	0 0
IOC	HA=11 (7%) VA=10 (6%)	HA=4 (12%) VA=3 (9%)

Pb Rate
3 Experiments:N=32

	165 Observations Within-session	32 Observations Between-session
Difference Score	0	0
Habituation Ratio	HA=7 (4%) VA=10 (6%)	0
Half-life	HA=7 (4%) VA=8 (5%)	0
IOC	HA=7 (4%) VA=5 (3%)	HA=12 (36%) VA=10 (30%)

Indicates that "1" was substituted for "0" if no activity occurred in the last testing interval.
Indicates that the majority of activity occurred during the first testing interval.
Indicates that the IOC was a positive number.

Table 8

0	1 Horiz Ratio	2 Vert Ratio	3 Horiz 1/2 Between	4 Vert 1/2 Between	5 IOC Horiz	6 IOC Vert
1	0.349487	0.168675	1.595476	1.309769	-0.195765	-0.307264
2	0.431917	0.225532	1.803708	1.454545	-0.135587	-0.290402
3	0.467911	0.265957	1.847367	1.523006	-0.131680	-0.233261
4	0.514150	0.288344	1.849629	1.543750	-0.117582	-0.232367
5	0.531530	0.300562	1.930721	1.629167	-0.115486	-0.206119
6	0.565858	0.319783	1.992540	1.741433	-0.110558	-0.190266
7	0.595499	0.347826	2.065684	1.767778	-0.110479	-0.182559
8	0.626646	0.419162	2.088776	1.777143	-0.107765	-0.181763
9	0.635107	0.419689	2.088923	1.786585	-0.105830	-0.173504
10	0.647179	0.434053	2.093683	1.839713	-0.095375	-0.173333
11	0.653415	0.445455	2.112106	1.841060	-0.090545	-0.154805
12	0.658377	0.445652	2.119511	1.863095	-0.085417	-0.151240
13	0.663477	0.459064	2.125726	1.894531	-0.080652	-0.140276
14	0.676327	0.471591	2.128145	1.900552	-0.078602	-0.138158
15	0.688860	0.474138	2.144631	1.984314	-0.072679	-0.124924
16	0.694321	0.474138	2.164676	2.023529	-0.069558	-0.119058
17	0.701898	0.535211	2.194990	2.035176	-0.066590	-0.095972
18	0.704759	0.551020	2.253601	2.134921	-0.064688	-0.095340
19	0.705039	0.598007	2.287889	2.176543	-0.063292	-0.091896
20	0.708763	0.633333	2.288571	2.205882	-0.060716	-0.091075
21	0.766834	0.654088	2.312451	2.223039	-0.060704	-0.076364
22	0.774057	0.662132	2.321336	2.223404	-0.055577	-0.069837
23	0.797992	0.666667	2.321577	2.242647	-0.048942	-0.067925
24	0.806191	0.705128	2.349709	2.259358	-0.048262	-0.067433
25	0.806191	0.708661	2.389965	2.260000	-0.047507	-0.066550
26	0.834549	0.708955	2.399750	2.272727	-0.037044	-0.052151
27	0.844909	0.767544	2.460030	2.370763	-0.027336	-0.047632
28	0.850869	0.771930	2.463475	2.461538	-0.012484	-0.045033
29	0.884045	0.785235	2.500000	2.500000	0.000000	-0.008565
30	0.932765	0.811594	2.534703	2.622715	0.012523	0.000000
31	1.004659	0.834286	2.639351	2.623684	0.027531	0.009195
32	1.314847	0.943548	2.718451	2.630631	0.044487	0.012353

Table 8. Between-session habituation measures for concurrent-control male Long Evans rats.

0	1 Horiz Ratio	2 Vert Ratio	3 Horiz 1/2 Between	4 Vert 1/2 Between	5 IOC Horiz	6 IOC Vert
1	0.429571	0.195804	1.982766	1.062500	-0.159080	-0.304523
2	0.438751	0.209836	2.014116	1.534091	-0.138795	-0.291579
3	0.503833	0.224490	2.027383	1.650000	-0.138298	-0.267089
4	0.576358	0.275362	2.100455	1.660606	-0.100520	-0.219144
5	0.581942	0.319392	2.101579	1.782555	-0.087341	-0.186039
6	0.591563	0.320000	2.144552	1.830909	-0.087291	-0.177243
7	0.672238	0.391924	2.152602	1.886423	-0.083618	-0.172255
8	0.682477	0.471698	2.170449	1.913669	-0.080120	-0.162985
9	0.742713	0.508850	2.173158	1.923077	-0.074933	-0.158961
10	0.746896	0.516129	2.219178	2.047203	-0.064587	-0.126689
11	0.747262	0.528986	2.261356	2.058719	-0.064579	-0.121176
12	0.754269	0.556391	2.268865	2.064220	-0.062925	-0.119431
13	0.756889	0.574661	2.297950	2.079710	-0.060293	-0.106865
14	0.779051	0.582840	2.303146	2.090000	-0.055717	-0.105618
15	0.789569	0.592920	2.303799	2.102122	-0.045678	-0.098723
16	0.796415	0.614555	2.322945	2.241379	-0.045378	-0.077241
17	0.819036	0.677273	2.327801	2.286585	-0.040496	-0.072429
18	0.851461	0.687361	2.334401	2.331818	-0.036461	-0.050562
19	0.893577	0.743151	2.368408	2.344262	-0.023094	-0.046647
20	0.924571	0.752475	2.391023	2.374593	-0.017157	-0.041128
21	0.948255	0.782895	2.492563	2.485075	0.006918	-0.036896
22	1.000530	0.808451	2.561415	2.550343	0.015857	-0.020866
23	1.067868	0.906977	2.610779	2.560000	0.030094	0.005333
24	1.133092	1.030928	2.633285	2.587607	0.039982	0.029758
25	1.161417	1.217391	2.732052	2.632686	0.040987	0.069872
26	1.438052	1.226667	2.811217	2.733096	0.043948	0.077149
27	1.457940	1.251656	2.871357	2.855140	0.056488	0.092271
28	1.518715	1.578947	2.873581	2.884058	0.085983	0.109385
29	1.522853	1.666667	3.004355	2.972763	0.088460	0.119325
30	1.564026	3.074074	3.251878	3.027682	0.149331	0.119864
31	1.813215	3.280488	3.276919	3.268817	0.230060	0.147872
32	4.243639	7.103448	4.315529	3.706612	0.565520	0.340373

Table 9. Between-session habituation measures for male Long Evans rats exposed postnatally to 0.2% lead in drinking water.

0	1 Horiz Ratio	2 Vert Ratio	3 Horiz 1/2 Between	4 Vert 1/2 Between	5 IOC Horiz	6 IOC Vert
1	0.315789	0.131868	1.484823	1.127027	-0.266119	-0.406241
2	0.357025	0.139818	1.732028	1.185000	-0.163995	-0.352258
3	0.476793	0.170213	1.931264	1.276190	-0.141707	-0.312690
4	0.501213	0.227437	1.993863	1.434673	-0.141251	-0.265912
5	0.518475	0.231102	2.011807	1.601190	-0.119091	-0.265868
6	0.547094	0.243697	2.029235	1.625000	-0.106022	-0.256344
7	0.566367	0.266160	2.031781	1.650407	-0.105337	-0.233628
8	0.572741	0.289855	2.036306	1.671795	-0.102081	-0.232153
9	0.586055	0.306878	2.039413	1.689119	-0.102081	-0.218809
10	0.596634	0.312500	2.097932	1.720588	-0.098916	-0.214000
11	0.603270	0.318766	2.102834	1.726000	-0.097843	-0.207663
12	0.621208	0.320346	2.107495	1.767241	-0.097679	-0.203243
13	0.630510	0.325843	2.168552	1.782918	-0.096211	-0.192970
14	0.633186	0.396429	2.171632	1.791667	-0.087633	-0.180125
15	0.657544	0.398936	2.187724	1.808824	-0.085952	-0.166071
16	0.661056	0.402367	2.190946	1.831797	-0.085503	-0.159681
17	0.661189	0.428571	2.219755	1.866667	-0.083868	-0.151974
18	0.669121	0.445783	2.236142	1.893365	-0.081703	-0.142294
19	0.670270	0.468208	2.236705	1.963710	-0.081312	-0.141523
20	0.673037	0.496970	2.243860	1.996644	-0.073108	-0.139717
21	0.687284	0.498127	2.255982	2.006276	-0.070885	-0.136416
22	0.688172	0.514403	2.256770	2.011706	-0.070060	-0.134969
23	0.694912	0.526690	2.268474	2.018717	-0.068588	-0.124725
24	0.697688	0.528889	2.272346	2.051220	-0.067486	-0.123898
25	0.700387	0.531073	2.282907	2.061224	-0.066951	-0.117826
26	0.723011	0.542234	2.297918	2.066929	-0.066028	-0.112711
27	0.734071	0.546875	2.299321	2.070064	-0.064039	-0.111449
28	0.743246	0.559028	2.302621	2.116667	-0.059401	-0.109217
29	0.744180	0.614035	2.306905	2.134752	-0.057615	-0.105995
30	0.757001	0.635193	2.314253	2.135484	-0.054800	-0.104377
31	0.767685	0.653509	2.318182	2.143519	-0.041556	-0.102660
32	0.811078	0.670300	2.334489	2.162562	-0.040080	-0.100990
33	0.829839	0.670886	2.335754	2.175000	-0.035497	-0.054545
34	0.840467	0.734426	2.370495	2.258454	-0.033986	-0.053353
35	0.848485	0.738938	2.372349	2.259669	-0.032282	-0.038378
36	0.867763	0.774566	2.373609	2.398148	-0.031943	-0.029039
37	0.868455	0.782609	2.450214	2.444444	-0.021666	-0.027350
38	0.869755	0.785000	2.480161	2.450820	-0.012161	-0.023706
39	0.877492	0.799065	2.487808	2.459620	-0.005928	-0.019672
40	0.915284	0.854749	2.546978	2.500000	0.000049	-0.013448
41	0.919704	0.881517	2.553959	2.509479	0.007207	-0.001069
42	0.954601	0.890909	2.554878	2.560172	0.010696	0.004819
43	0.975334	0.927350	2.562178	2.569767	0.011255	0.010380
44	1.021949	0.933610	2.576609	2.608949	0.012477	0.015044
45	1.042306	1.047945	2.599336	2.633080	0.015367	0.017464
46	1.084075	1.088235	2.600754	2.650000	0.015484	0.018200
47	1.115987	1.101351	2.614294	2.730769	0.022154	0.021891
48	1.153562	1.105634	2.635417	2.779279	0.037308	0.052017
49	1.178862	1.159624	2.645857	2.783019	0.039456	0.074194
50	1.193093	1.311594	2.688569	2.892473	0.046676	0.076586
51	1.202163	1.550336	2.713052	3.005906	0.056008	0.106921
52	1.231099	1.692623	2.761323	3.067925	0.059734	0.134280
53	1.258676	1.766667	2.812024	3.201220	0.062749	0.146614
54	1.434958	1.795775	2.919842	3.224189	0.066787	0.152663

Table 10. Between-session habituation measures for historical-control male Long Evans rats.

Table 11. CONCURRENT CONTROL VALUES EXPRESSED AS Z SCORES

	Habituation Ratio Horizontal	Habituation Ratio Vertical	1/2 Between Horizontal	1/2 Between Vertical	IOC Horizontal	IOC Vertical
1	-2.013884	-1.7751256	-2.458096	-2.0863743	-2.5232072	-2.267767
2	-1.5584696	-1.5802241	-1.625168	-1.672786	-1.3244422	-2.0631311
3	-1.3596077	-1.3771005	-1.450532	-1.4771257	-1.2466135	-1.3696723
4	-1.1041436	-1.264603	-1.441484	-1.4178571	-0.9657769	-1.3588228
5	-1.0081215	-1.203206	-1.117116	-1.1738086	-0.9240239	-1.0412791
6	-0.8184641	-1.1066181	-0.89984	-0.8530486	-0.8258566	-0.8478884
7	-0.6547017	-0.9656985	-0.577264	-0.7777771	-0.8242829	-0.7543568
8	-0.4826188	-0.6072261	-0.484896	-0.75102	-0.7702191	-0.7446966
9	-0.4358729	-0.6045779	-0.484308	-0.7240429	-0.7316733	-0.644466
10	-0.3691768	-0.532397	-0.465268	-0.5722486	-0.5234064	-0.6423908
11	-0.3347238	-0.4751005	-0.391956	-0.5684	-0.4271912	-0.4175364
12	-0.3073094	-0.4741106	-0.361956	-0.5054429	-0.3250398	-0.3742718
13	-0.2791326	-0.4067136	-0.337096	-0.4156257	-0.2301195	-0.241236
14	-0.2081381	-0.3437638	-0.32742	-0.3984229	-0.1892829	-0.2155097
15	-0.138895	-0.3309648	-0.261476	-0.1591029	-0.0712948	-0.0549029
16	-0.1087238	-0.3309648	-0.181296	-0.04706	-0.0091235	0.0162864
17	-0.0668619	-0.0240653	-0.06004	-0.0137829	0.05	0.2964563
18	-0.0510552	0.0553769	0.174404	0.2712029	0.0878884	0.3041262
19	-0.0495083	0.2914925	0.311556	0.3901229	0.1156972	0.3459223
20	-0.0289337	0.4690101	0.314284	0.4739486	0.167012	0.3558859
21	0.2919006	0.5733065	0.409804	0.5229686	0.167251	0.5344175
22	0.3318066	0.6137286	0.445344	0.5240114	0.2693825	0.6136286
23	0.4640442	0.6365176	0.446308	0.5789914	0.4015538	0.6368325
24	0.5093425	0.8297889	0.558836	0.6267371	0.4150996	0.6428034
25	0.5093425	0.8475427	0.71986	0.6285714	0.4301394	0.6535194
26	0.6660166	0.8490201	0.759	0.6649343	0.6385657	0.8282646
27	0.7232541	1.1434372	1.00012	0.9450371	0.8319522	0.8831068
28	0.7561823	1.1654774	1.0139	1.2043943	1.1278088	0.9146845
29	0.9394757	1.2323367	1.16	1.3142857	1.376494	1.3572209
30	1.2086464	1.364794	1.298812	1.6649	1.6259562	1.461165
31	1.6058508	1.5488737	1.717404	1.6676686	1.9249203	1.5724549
32	3.3195967	2.0278794	2.033804	1.6875171	2.2626892	1.610801

Table 11. Concurrent control values expressed as Z scores based on an arbitrary criterion of z=1.65 representing reduced habituation in an estimated 5% of concurrent control rats.

Table 12. Pb VALUES EXPRESSED AS Z SCORES BASED ON CONCURRENT CONTROL VALUES

	Habituation Ratio Horizontal	Habituation Ratio Vertical	1/2 Between Horizontal	1/2 Between Vertical	IOC Horizontal	IOC Vertical
1	-1.5714309	-1.7296281	-0.908936	-2.7928571	-1.7924303	-2.2345024
2	-1.5207127	-1.6591156	-0.783536	-1.4454543	-1.3883466	-2.077415
3	-1.1611436	-1.5854774	-0.730468	-1.1142857	-1.3784462	-1.7802063
4	-0.760453	-1.3298392	-0.43818	-1.0839829	-0.6258964	-1.1983495
5	-0.7296022	-1.1085829	-0.433684	-0.7355571	-0.3633665	-0.7965898
6	-0.6764475	-1.1055276	-0.261792	-0.5974029	-0.3623705	-0.6898422
7	-0.2307293	-0.7441005	-0.229592	-0.4387914	-0.2892032	-0.6293083
8	-0.1741602	-0.3432261	-0.158204	-0.3609457	-0.2195219	-0.5168083
9	0.1586354	-0.1565327	-0.147368	-0.3340657	-0.1161952	-0.4679733
10	0.1817459	-0.1199548	0.036712	-0.02058	0.0899004	-0.0763228
11	0.183768	-0.0553467	0.205424	-0.0534829	0.0900598	-0.0094175
12	0.2224807	0.0823668	0.23546	0.0692	0.123008	0.0117597
13	0.2369558	0.1741759	0.3518	0.1134571	0.1754383	0.1642597
14	0.3593978	0.2152764	0.372584	0.1428571	0.2665936	0.1793932
15	0.4175083	0.2659297	0.375196	0.1774914	0.4665737	0.2630704
16	0.4553315	0.3746482	0.45178	0.5753686	0.4725498	0.5237743
17	0.5803094	0.6898141	0.471204	0.7045286	0.5698008	0.5821723
18	0.759453	0.7405075	0.497604	0.8337657	0.6501793	0.8475485
19	0.9921381	1.0208593	0.633632	0.86932	0.9164542	0.8950607
20	1.1633757	1.0677136	0.724092	0.95598	1.0347211	0.9620388
21	1.2942265	1.2205779	1.130252	1.2716429	1.5143028	1.0133981
22	1.5830387	1.349	1.40566	1.4581229	1.6923705	1.2079369
23	1.9550718	1.8441055	1.603116	1.4857143	1.9759761	1.5258859
24	2.3154254	2.4669749	1.69314	1.5645914	2.1729482	1.8223058
25	2.4719171	3.4039749	2.088208	1.6933886	2.1929681	2.3091262
26	4.0002873	3.4505879	2.404868	1.9802743	2.2519522	2.3974393
27	4.1101657	3.5761608	2.645428	2.3289714	2.501753	2.5809587
28	4.4459392	5.2208392	2.654324	2.4115943	3.0893028	2.7886529
29	4.468801	5.6616432	3.17742	2.6650371	3.1386454	2.909284
30	4.692762	12.73404	4.167512	2.8219486	4.3512151	2.9158252
31	6.073011	13.771286	4.267676	3.5109057	5.9593625	3.2557282
32	19.500768	32.982151	8.422116	4.7617486	12.641833	5.5919053

Table 12. Pb values expressed as Z scores, after adjustment for displacement of the distribution, relative to concurrent control values.

Table 13. HISTORICAL CONTROL VALUES EXPRESSED AS Z SCORES

	Habituation Ratio Horizontal	Habituation Ratio Vertical	1/2 Between Horizontal	1/2 Between Vertical	IOC Horizontal	IOC Vertical
1	-1.9967125	-1.3336569	-3.0932481	-2.1081082	-3.3475154	-2.4589252
2	-1.8248958	-1.3141716	-2.1776741	-1.9897959	-1.7715278	-2.0291242
3	-1.3258625	-1.239674	-1.439763	-1.8036939	-1.4275772	-1.7140924
4	-1.2241125	-1.0994191	-1.2079148	-1.4802595	-1.4205401	-1.7140924
5	-1.1521875	-1.0904363	-1.1414556	-1.1404286	-1.0785648	-1.3416561
6	-1.0329417	-1.0595663	-1.0769074	-1.0918367	-0.8768827	-1.2654777
7	-0.9526375	-1.0045098	-1.0674778	-1.0399857	-0.8663117	-1.0846178
8	-0.9260792	-0.9464338	-1.0507185	-0.9963367	-0.8160648	-1.0728742
9	-0.8706042	-0.9047108	-1.0392111	-0.9609582	-0.8160648	-0.9666322
10	-0.826525	-0.8909314	-0.8224741	-0.8967592	-0.7672222	-0.928944
11	-0.796875	-0.8755735	-.8043185	-0.8857143	-0.7506636	-0.8778901
12	-0.7241333	-0.871701	-0.7870556	-0.801549	-0.7481327	-0.842699
13	-0.685375	-0.8582279	-0.5609185	-0.7695551	-0.7254784	-0.7609076
14	-0.674225	-0.685223	-0.5495111	-0.7517	-0.5931019	-0.6586385
15	-0.5727333	-0.6790784	-0.4899111	-0.7166857	-0.5671605	-0.5467436
16	-0.5576833	-0.6706691	-0.4779778	-0.669802	-0.5602315	-0.4958678
17	-0.5575833	-0.6064436	-0.3712778	-0.5986388	-0.535	-0.4345064
18	-0.5244958	-0.5642574	-0.3105852	-0.5441531	-0.5015895	-0.3574363
19	-0.5197083	-0.5092941	-0.3085	-0.4005918	-0.4955556	-0.3512978
20	-0.5081792	-0.438799	-0.282	-0.3333796	-0.3669506	-0.3369188
21	-0.4488167	-0.4359632	-0.2371037	-0.3137225	-0.3346451	-0.3106369
22	-0.4451167	-0.3960711	-0.2341852	-0.3026408	-0.3219136	-0.2991162
23	-0.4170333	-0.3659559	-0.190837	-0.2883327	-0.2991975	-0.2175557
24	-0.4054667	-0.3605662	-0.1764963	-0.222	-0.2821914	-0.2109713
25	-0.3942208	-0.3552132	-0.1373815	-0.2015837	-0.2739352	-0.1626274
26	-0.2999542	-0.3278578	-0.0817852	-0.1899408	-0.2596914	-0.1219029
27	-0.2538708	-0.3164828	-0.0765889	-0.1835429	-0.2289969	-0.118551
28	-0.2156417	0.2866961	-0.0643667	-0.0884347	-0.1574228	-0.0940844
29	-0.21175	-0.151875	-0.0485	-0.0515265	-0.1298611	-0.0684315
30	-0.1583292	-0.1000172	-0.0212852	-0.0500327	-0.0864198	-0.055549
31	-0.1138125	-0.0992426	-0.0067333	-0.0336347	0.117963	-0.041879
32	0.0669917	-0.0139706	0.053663	0.0052286	0.1407407	-0.0285828
33	0.1451625	-0.0125343	0.0583481	0.0306122	0.2114661	0.03412022
34	0.1894458	0.143201	0.1870185	0.2009265	0.234784	0.3506927
35	0.2228542	0.1542598	0.1938852	0.2034061	0.2610803	0.4699204
36	0.3031792	0.2415833	0.1985519	0.4860163	0.2663117	0.5442755
37	0.3060625	0.2612966	0.4822741	0.580498	0.4249074	0.5577229
38	0.3114792	0.2671569	0.5931889	0.5935102	0.5715895	0.5867357
39	0.3437167	0.3016299	0.6215111	0.6114694	0.6677778	0.6188535
40	0.5011833	0.4381103	0.8406593	0.6938776	0.7600154	0.6684076

Table 13. Historical control values expressed as Z scores based on an arbitrary criterion of Z = 1.65 representing reduced habituation in an estimated 5% of the historical control rats.

Table 13. HISTORICAL CONTROL VALUES EXPRESSED AS Z SCORES

41	0.5196017	0.5037181	0.8665148	0.7132225	0.8704784	0.7669666
42	0.6650042	0.5267378	0.8699185	0.816776	0.924321	0.8138455
43	0.7513917	0.6160539	0.8969556	0.8362592	0.9329475	0.858121
44	0.9456208	0.6313971	0.9504037	0.9162225	0.9518056	0.8952548
45	1.0304417	0.9116299	1.0345778	0.9654694	0.9964043	0.9145223
46	1.2044792	1.0103799	1.0398296	1	0.9982099	0.9203822
47	1.334458	1.042527	1.0899778	1.1648347	1.101142	0.9497691
48	1.4940083	1.0530245	1.1682111	1.2638347	1.335	1.1896258
49	1.599425	1.1853529	1.2068778	1.2714673	1.3681481	1.3661943
50	1.6587208	1.5578284	1.3650704	1.4948429	1.4795679	1.3852389
51	1.6965125	2.1429804	1.6715007	1.7263388	1.6235802	1.6267596
52	1.8170792	2.491723	1.6345296	1.8529082	1.6810802	1.844586
53	1.9319833	2.6732034	1.8223111	2.1249388	1.727608	1.9427866
54	2.6664917	2.7445466	2.221637	2.1718143	1.7899228	1.9909475

Table 13. Historical control values expressed as Z scores based on an arbitrary criterion of Z = 1.65 representing reduced habituation in an estimated 5% of the historical control rats.

Table 14. Pb VALUES EXPRESSED AS Z SCORES BASED ON HISTORICAL CONTROL VALUES

	Habituation Ratio Horizontal	Habituation Ratio Vertical	1/2 Between Horizontal	1/2 Between Vertical	IOC Horizontal	IOC Vertical
1	-1.5226208	-1.176951	-1.2490148	-2.2397959	-1.695679	-1.6490685
2	-1.4843708	-1.1425588	-1.1329037	-1.2773653	-1.3826389	-1.5460111
3	-1.213958	-1.1066422	-1.0837667	-1.0408163	-1.3749691	-1.3510271
4	-0.9110083	-0.9819559	-0.8131296	-1.0191714	-0.7919753	-0.9692994
5	-0.8877417	-0.8740392	-0.8089667	-0.7702959	-0.5885957	-0.7057254
6	-0.8476542	-0.872549	-0.6498074	-0.6716143	-0.5878241	-0.6356927
7	-0.5115083	-0.6962647	-0.619926	-0.5583204	-0.531142	-0.5959793
8	-0.4688458	-0.5007402	-0.5538926	-0.5027206	-0.4771605	-0.5221736
9	-0.2178625	-0.4096814	-0.5438593	-0.4835163	-0.3971142	-0.4901354
10	-0.2004333	-0.3918407	-0.3734148	-0.230198	-0.2374537	-0.2331927
11	-0.1989083	-0.3603284	-0.2172	-0.2066959	-0.2373303	-0.1892994
12	-0.1697125	-0.2931593	-0.1893889	-0.1954694	-0.2118056	-0.1754061
13	-0.1587958	-0.2483799	-0.0816667	-0.1638571	-0.1711883	-0.0753583
14	-0.0664542	-0.2283333	-0.0624222	-0.1428571	-0.100571	-0.0654299
15	-0.0226292	-0.2036275	-0.0600037	-0.1181184	0.0543519	-0.0105334
16	0.0058958	-0.1506005	-0.0109074	0.4109776	0.0589815	0.01605016
17	0.10015	0.0031201	0.0288926	0.2583367	0.134321	0.1988137
18	0.2352542	0.0278456	0.053337	0.350649	0.1965895	0.372914
19	0.4107375	0.1645858	0.1792889	0.3760449	0.4028704	0.4040844
20	0.5398792	0.1874387	0.2630482	0.4379449	0.4944907	0.4480255
21	0.6385625	0.2619976	0.6391222	0.6634184	0.8660185	0.4817198
22	0.856375	0.3246348	0.8941296	0.7966184	1.003966	0.6093471
23	1.13695	0.5661201	1.0769593	0.8163265	1.2236728	0.8179379
24	1.4087167	0.8699216	1.1603148	0.8726674	1.3762654	1.0124045
25	1.5267375	1.3269387	1.5261185	0.9646653	1.3917747	1.3317834
26	2.6793833	1.349674	1.8193222	1.1695837	1.4374691	1.3897213
27	2.76225	1.4109216	2.042063	1.4186531	1.6309877	1.5101194
28	3.0154792	2.2131054	2.0503	1.4776694	2.0861574	1.6463774
29	3.0327208	2.4281054	2.5346481	1.6587	2.1243827	1.7255175
30	3.204275	5.8776324	3.4514	1.7707796	3.06375	1.7298089
31	4.2425625	6.383549	3.5441444	2.2628918	4.3095679	1.9528025
32	14.369329	15.753549	7.3908481	3.156351	9.4864198	3.4854538

Table 14. Pb values expressed as Z scores, after adjustment for displacement of the distribution, relative to historical control values

Table 15. RELATIVE RISK FOR PB RATS BASED ON REDUCED HABITUATION IN AN ESTIMATED 5% OF CONTROL RATS

	Control	Historical Control
Horizontal Habituation Ratio	10	2.4
Vertical Habituation Ratio	10	*5
Horizontal 1/2 Between	4.5	5.9
Vertical 1/2 Between	2.7	1.7
Horizontal IOC	5.5	1.4
Vertical IOC	*9	2.3

Table 15. Relative risk(RR) ratios for Pb rats are based on an arbitrary criterion of z=1.65 representing reduced habituation in an estimated 5% of the concurrent and historical control rat populations, respectively. These RR ratios were calculated based on raw or actual habituation measures.

*indicates that all of the control rats habituated Consequently, RR were calculated based on 1 control rat failing to habituate.

Table 16. RELATIVE RISK FOR Pb RATS BASED ON REDUCED HABITUATION IN AN ESTIMATED 10% OF CONTROL RATS

	Control	Historical Control
Horizontal Habituation Ratio	6	1.9
Vertical Habituation Ratio	3.7	1
Horizontal 1/2 Between	3.7	2.7
Vertical 1/2 Between	3	1.4
Horizontal OC	3	2.2
Vertical OC	2.5	2.3

Table 16. Relative risk (RR) ratios for Pb rats are based on an arbitrary criterion of z=1.25 representing reduced habituation in an estimated 10% of the concurrent and historical control rat populations, respectively. These RR ratios were calculated based on raw or actual habituation measures.

Table 17. RELATIVE RISK FOR Pb RATS BASED ON REDUCED HABITUATION IN AN ESTIMATED 5% OF CONTROL RATS

	Control	Historical Control
Horizontal Habituation Ratio	24	3.7
Vertical Habituation Ratio	25.2	3.8
Horizontal 1/2 Between	7	8.4
Vertical 1/2 Between	4.3	2.5
Horizontal IOC	7	6.2
Vertical IOC	*14	3.9

Table 17. Relative risk (RR) ratios for Pb rats are based on an arbitrary criterion of z=1.65 representing reduced habituation in an estimated 5% of the concurrent and historical control rat populations, respectively. Pb values were then adjusted for displacement of their distribution relative to concurrent and historical control values in order to estimate the corresponding frequency of reduced habituation in Pb rats. These RR ratios were calculated based on distributions of habituation measures which were transformed to Z-scores.

* indicates that all of the control rats habituated. Consequently, RR were calculated based on 1 control rat failing to habituate.

Table 18. RELATIVE RISK FOR Pb RATS BASED ON REDUCED HABITUATION IN AN ESTIMATED 10% OF CONTROL RATS

	Control	Historical Control
Horizontal Habituation Ratio	3	3
Vertical Habituation Ratio	1.3	3.4
Horizontal 1/2 Between	3.3	1.1
Vertical 1/2 Between	3.8	1.9
Horizontal IOC	2.3	2.9
Vertical IOC	3.8	2.5

Table 18. Relative risk (RR) ratios for Pb rats are based on an arbitrary criterion of z=1.25 representing reduced habituation in an estimated 10% of the concurrent and historical control rat populations, respectively. Pb values were then adjusted for displacement of their distribution relative to concurrent and historical control values in order to estimate the corresponding frequency of reduced habituation in Pb rats. These RR ratios were calculated based on distributions of habituation measures which were transformed to Z-scores.

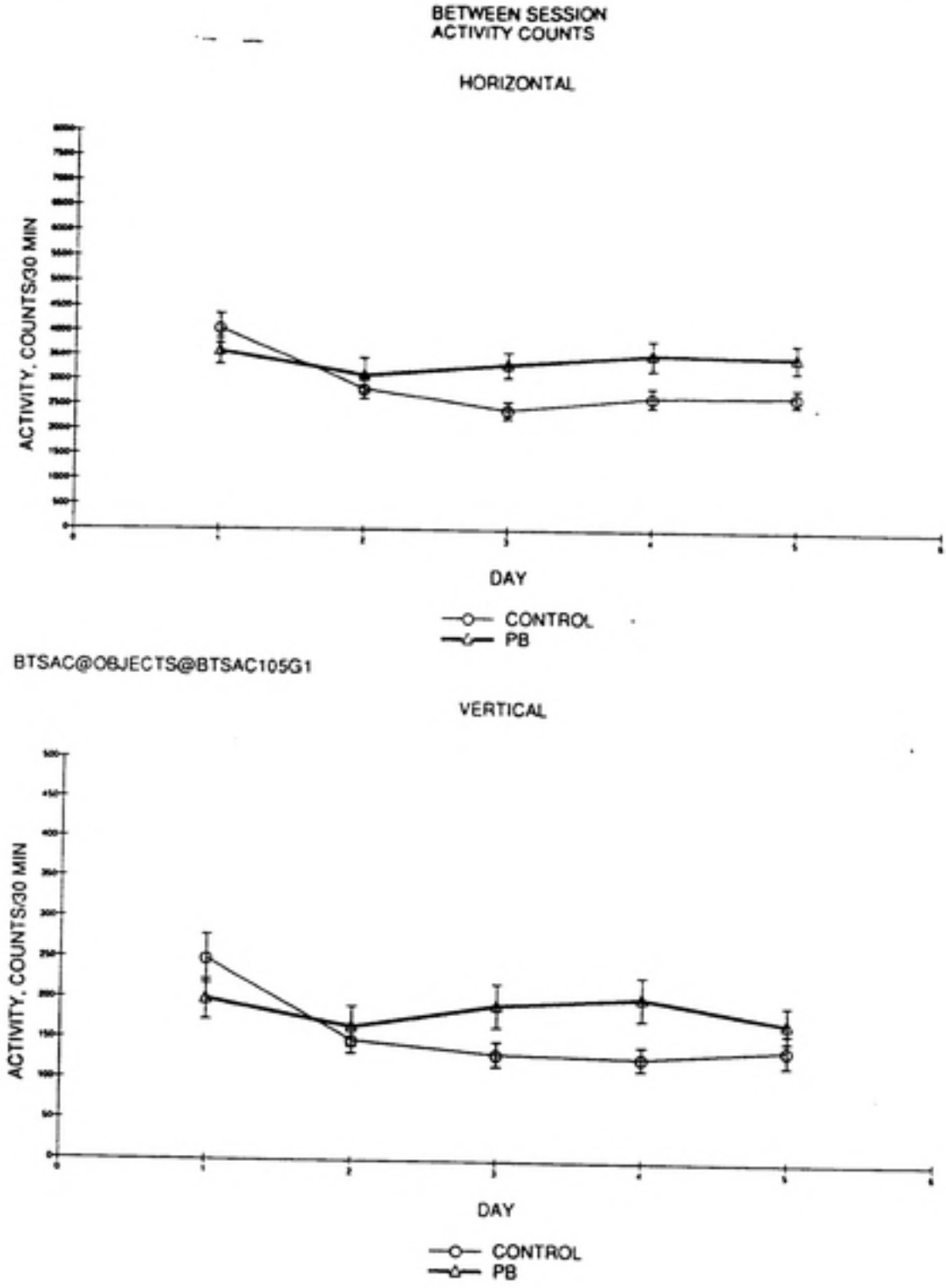

Fig. 2. Mean number of horizontal (top) and vertical (bottom) photocell counts in experiment 105 for Male Long Evans rats ingesting 0.2% lead acetate (N=12) or water (N=12) in five daily 30 minute tests.

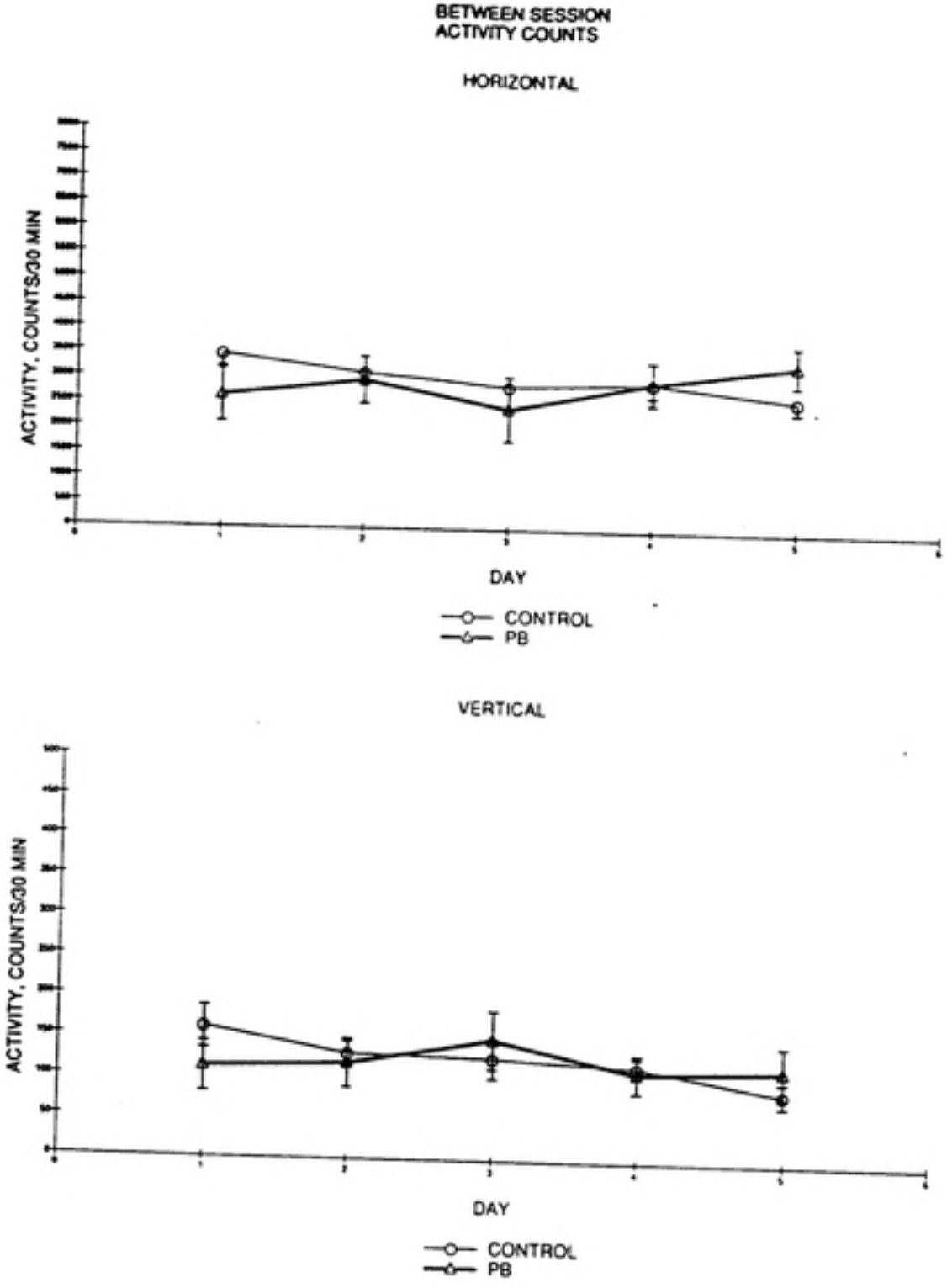

Fig. 3. Mean number of horizontal (top) and vertical (bottom) photocell counts in experiment 122 for Male Long Evans rats ingesting 0.2% lead acetate (N=8) or water (N=9) in five daily 30 minute tests.

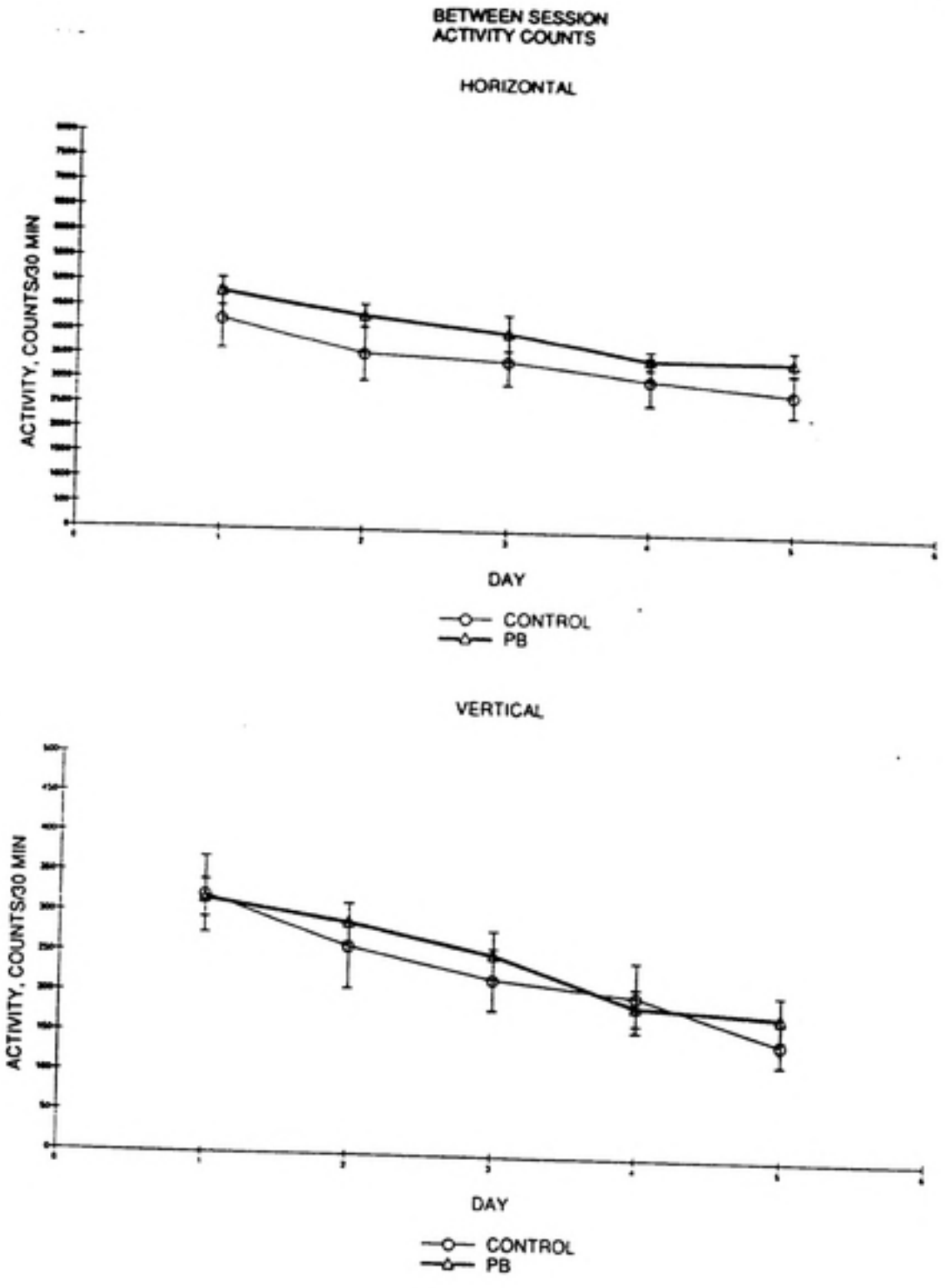

Fig. 4. Mean number of horizontal (top) and vertical (bottom) photocell counts in experiment 130 for Male Long Evans rats ingesting 0.2% lead acetate (N=12) or water (N=11) in five daily 30 minute tests.

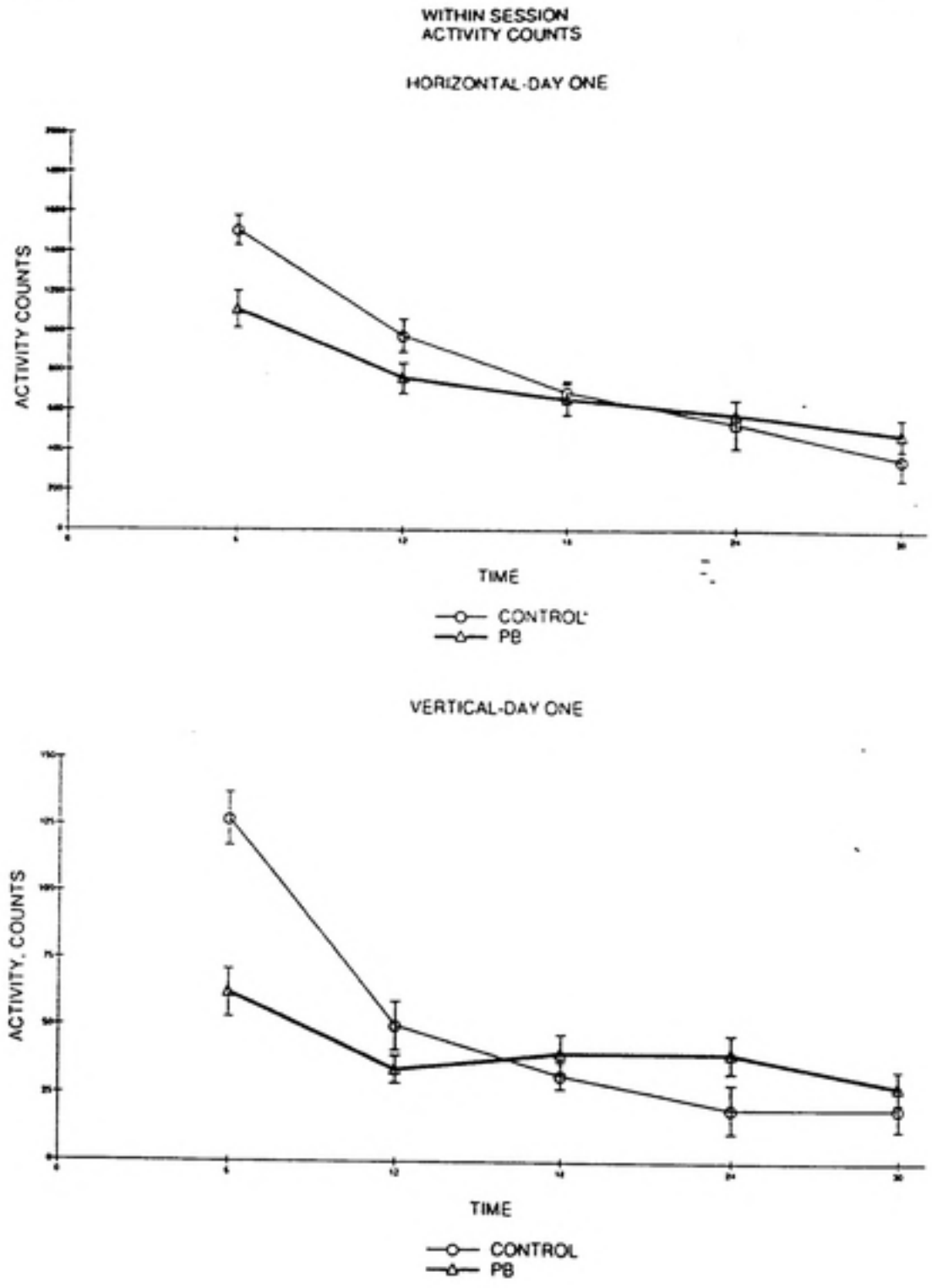

Fig. 5. Mean number of horizontal (top) and vertical (bottom) photocell counts in experiment 105 for Male Long Evans rats ingesting 0.2% lead acetate (N=12) or water (N=12) in five 6-minute intervals on day one of testing.

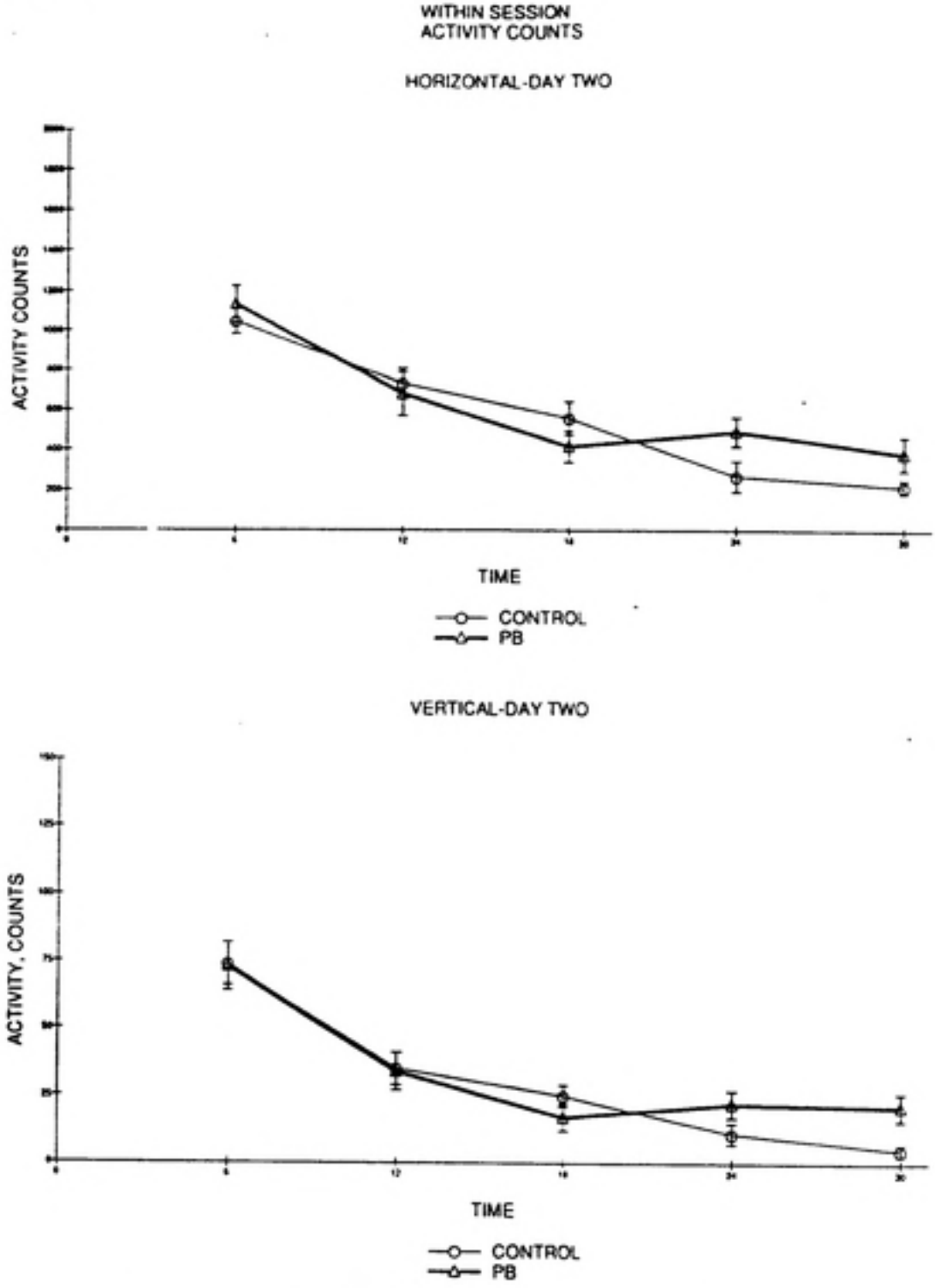

Fig. 6. Mean number of horizontal (top) and vertical (bottom) photocell counts in experiment 105 for Male Long Evans rats ingesting 0.2% lead acetate (N=12) or water (N=12) in five 6-minute intervals on day two of testing.

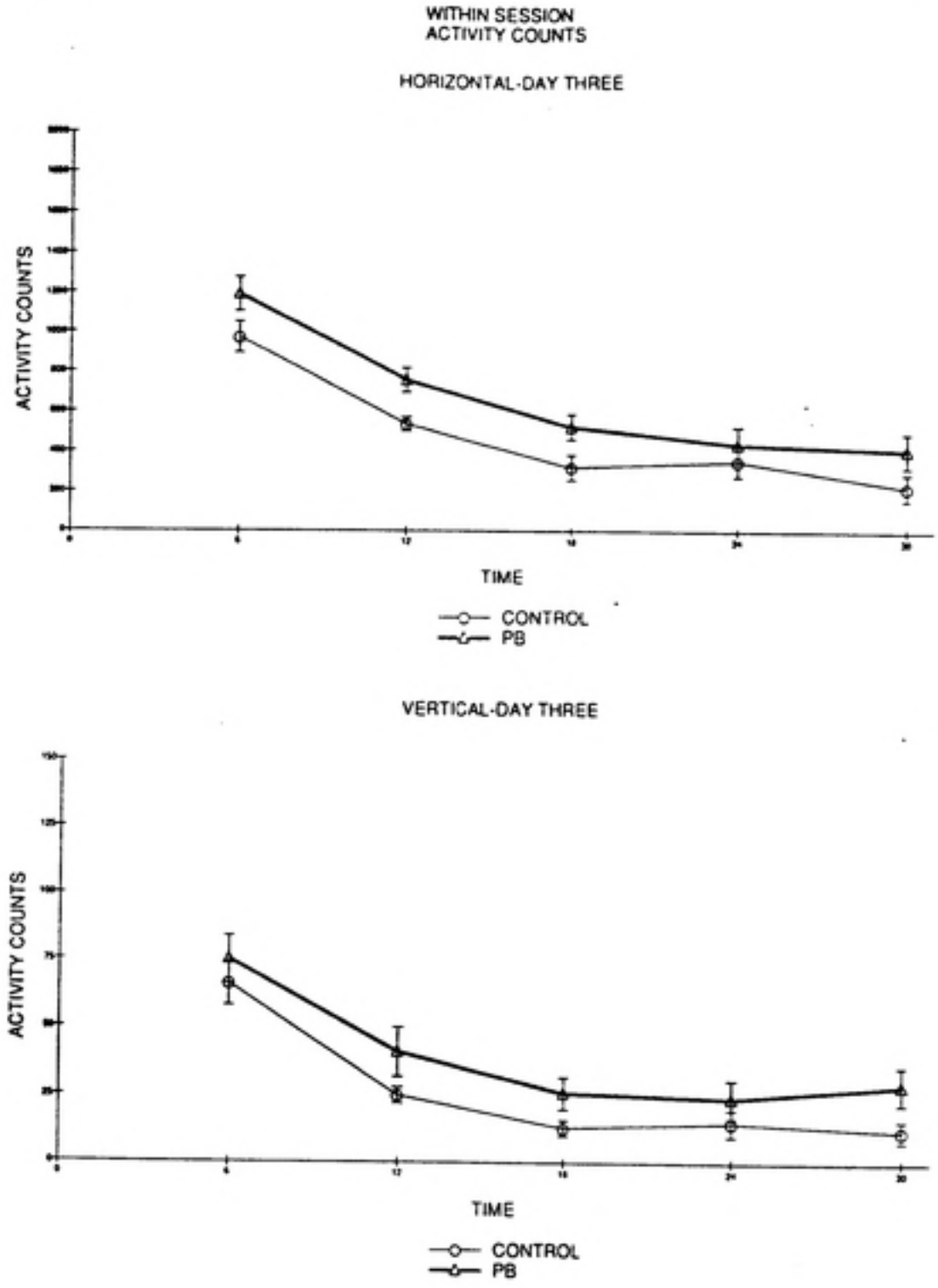

Fig. 7. Mean number of horizontal (top) and vertical (bottom) photocell counts in experiment 105 for Male Long Evans rats ingesting 0.2% lead acetate (N=12) or water (N=12) in five 6-minute intervals on day three of testing.

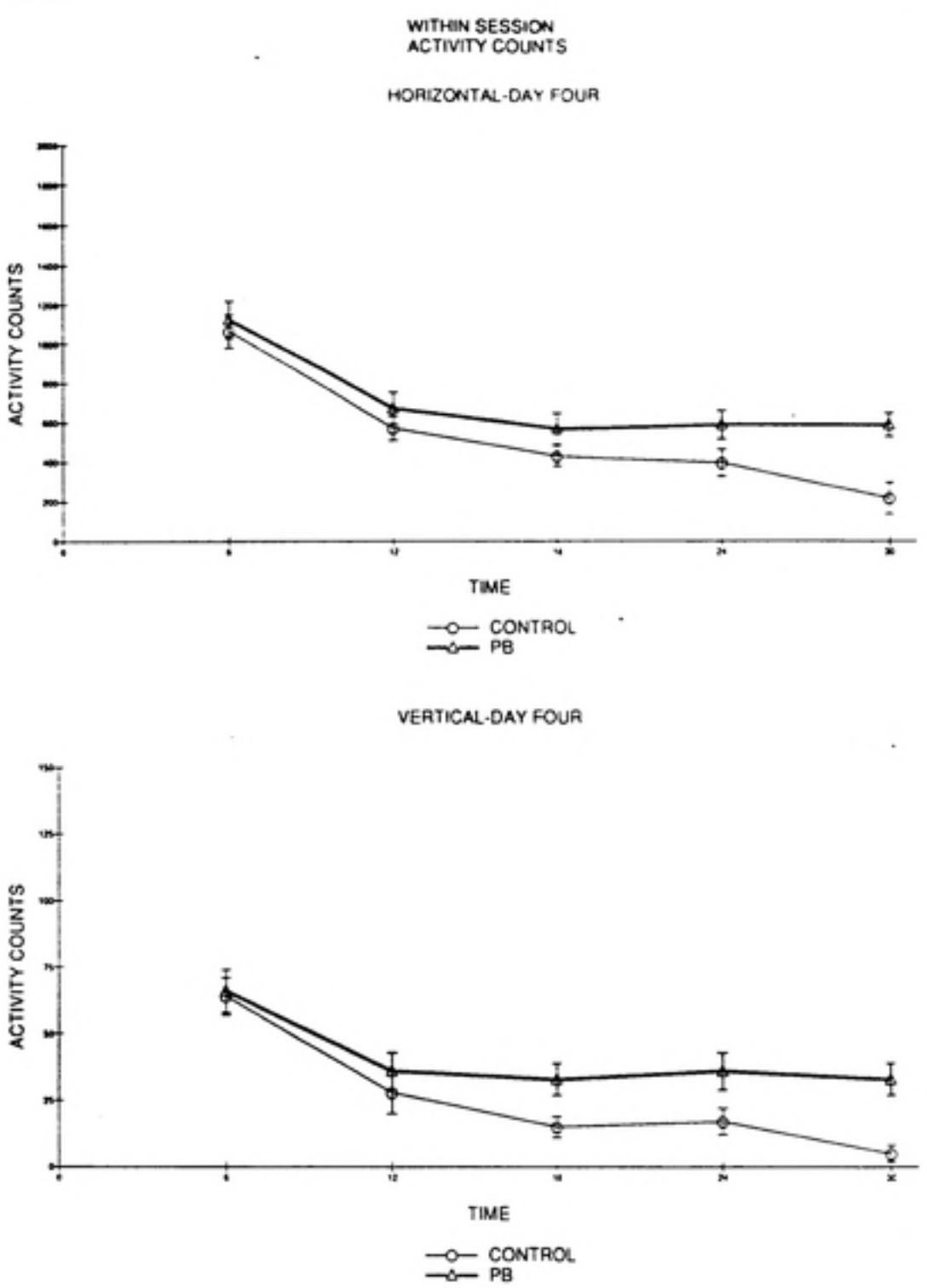

Fig. 8. Mean number of horizontal (top) and vertical (bottom) photocell counts in experiment 105 for Male Long Evans rats ingesting 0.2% lead acetate (N=12) or water (N=12) in five 6-minute intervals on day four of testing.

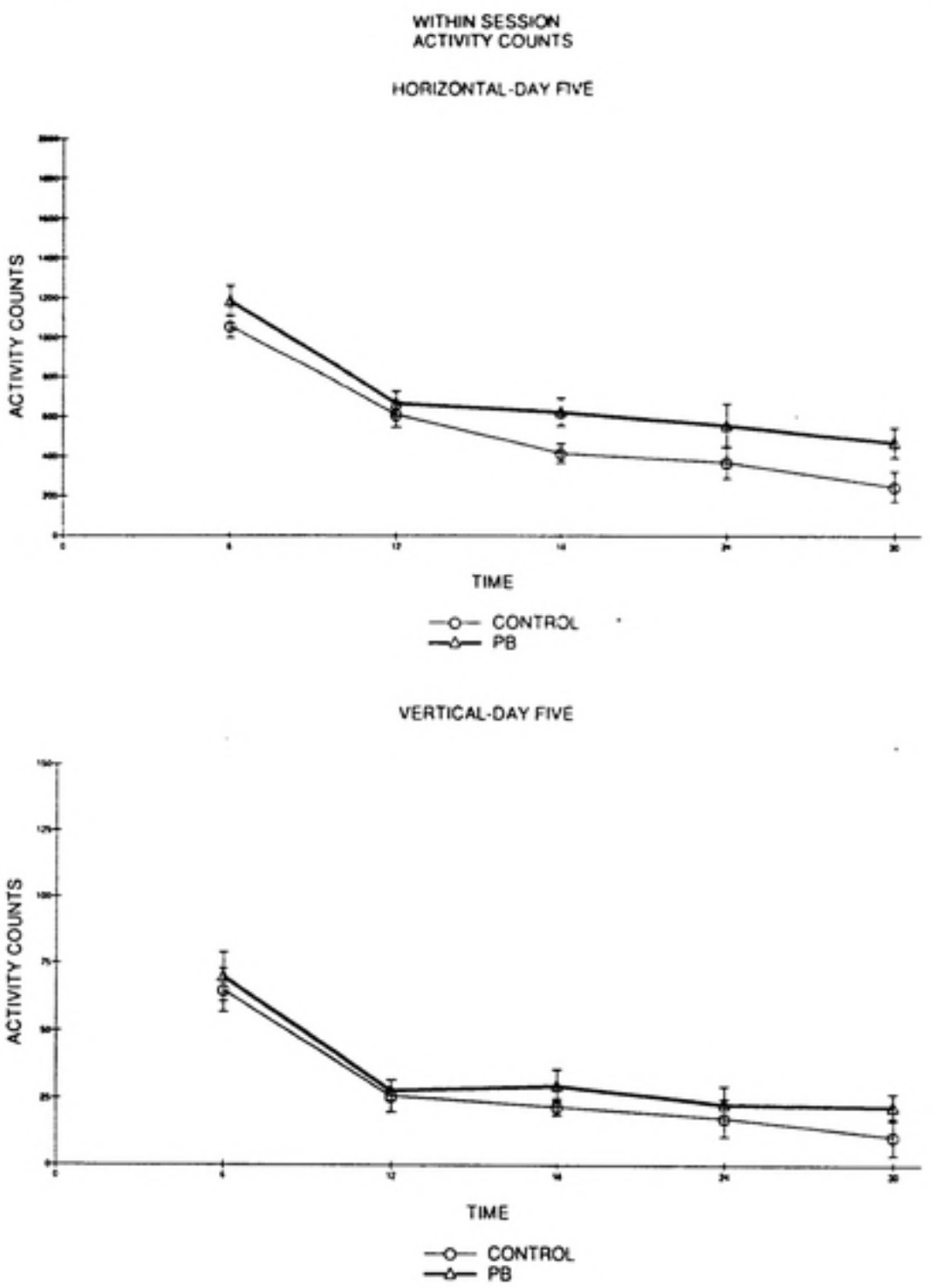

Fig. 9. Mean number of horizontal (top) and vertical (bottom) photocell counts in experiment 105 for Male Long Evans rats ingesting 0.2% lead acetate (N=12) or water (N=12) in five 6-minute intervals on day five of testing.

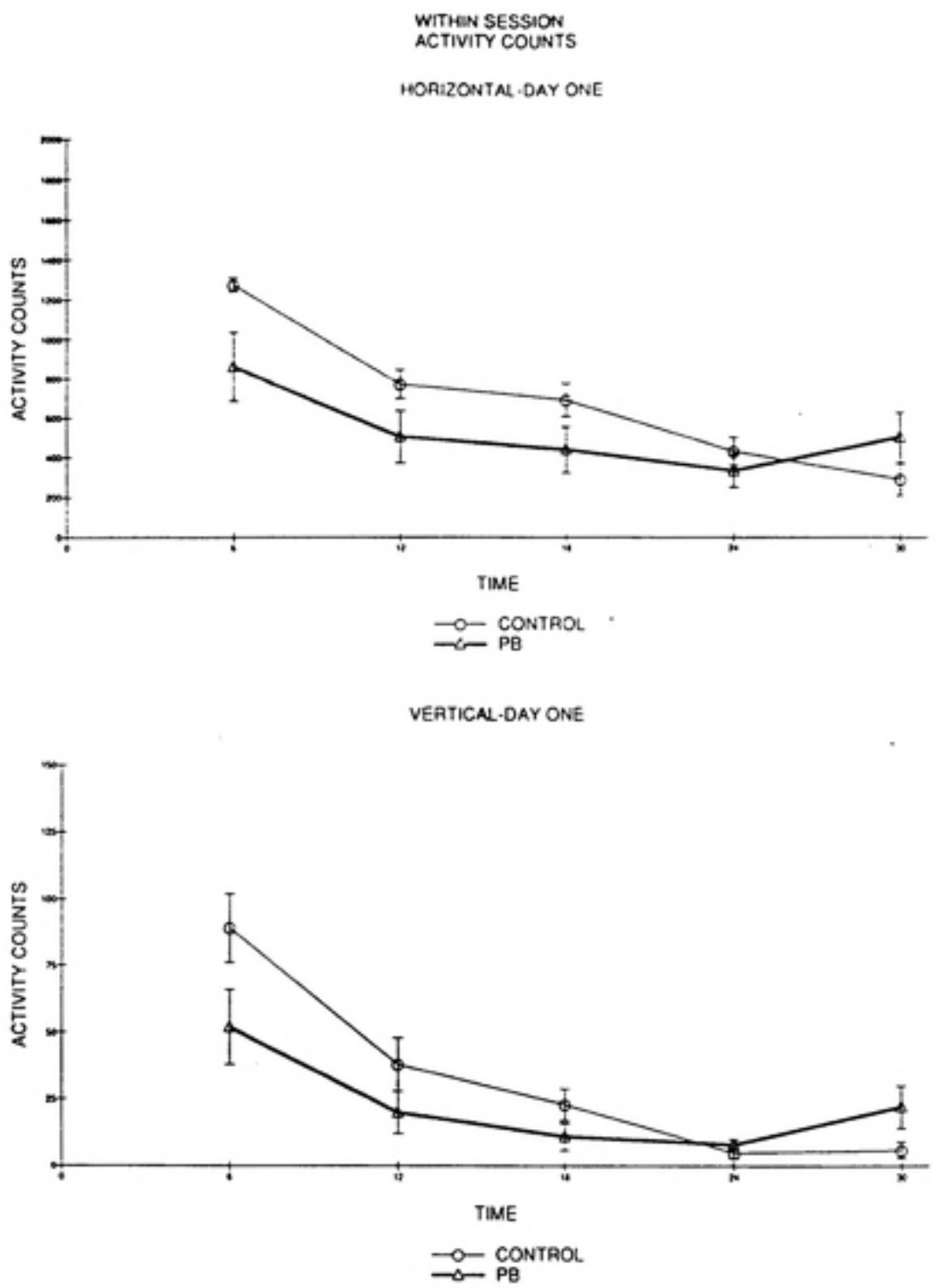

Fig. 10. Mean number of horizontal (top) and vertical (bottom) photocell counts in experiment 122 for Male Long Evans rats ingesting 0.2% lead acetate (N=8) or water (N=9) in five 6-minute intervals on day one of testing.

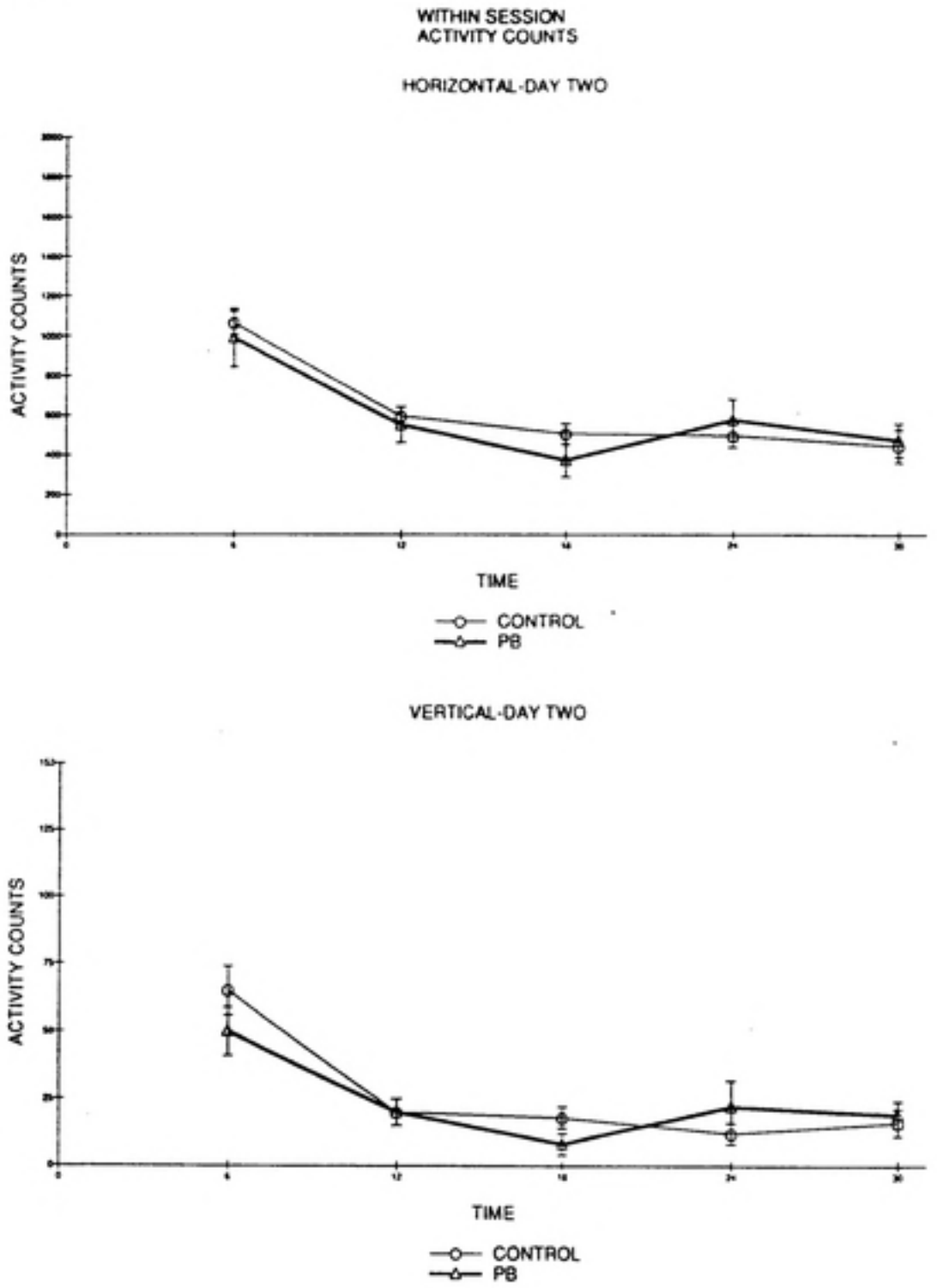

Fig. 11. Mean number of horizontal (top) and vertical (bottom) photocell counts in experiment 122 for Male Long Evans rats ingesting 0.2% lead acetate (N=8) or water (N=9) in five 6-minute intervals on day two of testing.

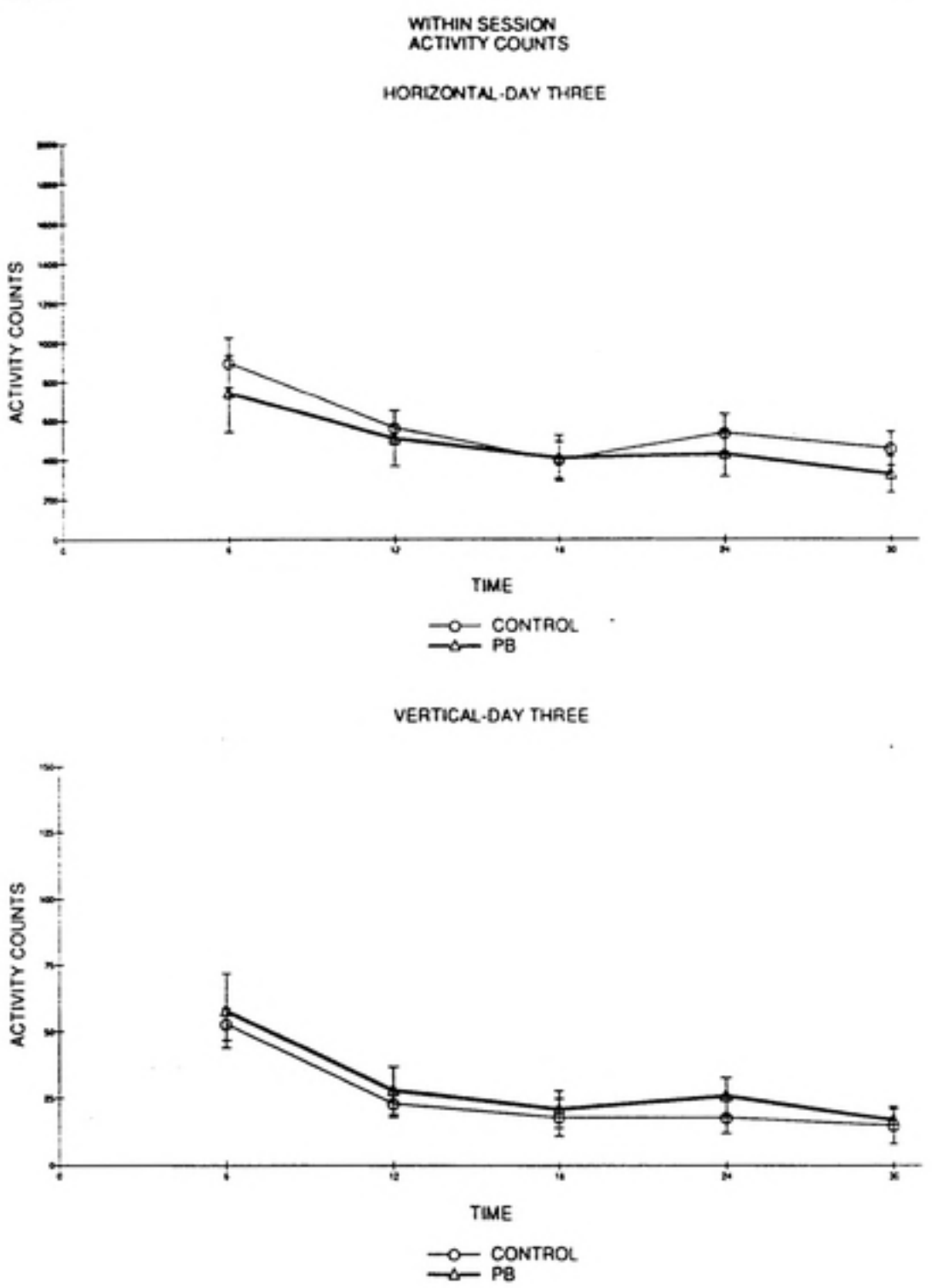

Fig. 12. Mean number of horizontal (top) and vertical (bottom) photocell counts in experiment 122 for Male Long Evans rats ingesting 0.2% lead acetate (N=8) or water (N=9) in five 6-minute intervals on day three of testing.

WS122

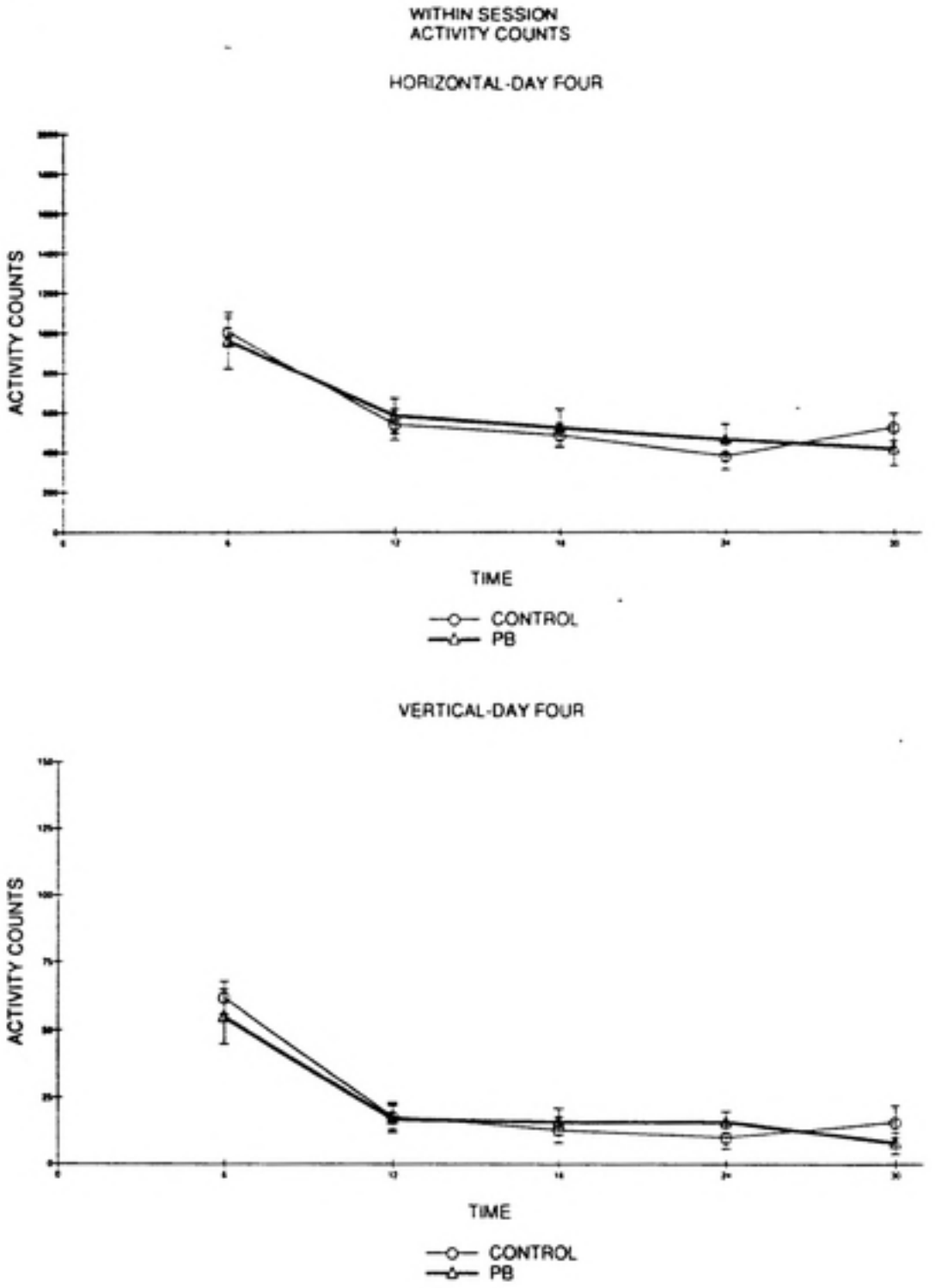

Fig. 13. Mean number of horizontal (top) and vertical (bottom) photocell counts in experiment 122 for Male Long Evans rats ingesting 0.2% lead acetate (N=8) or water (N=9) in five 6-minute intervals on day four of testing.

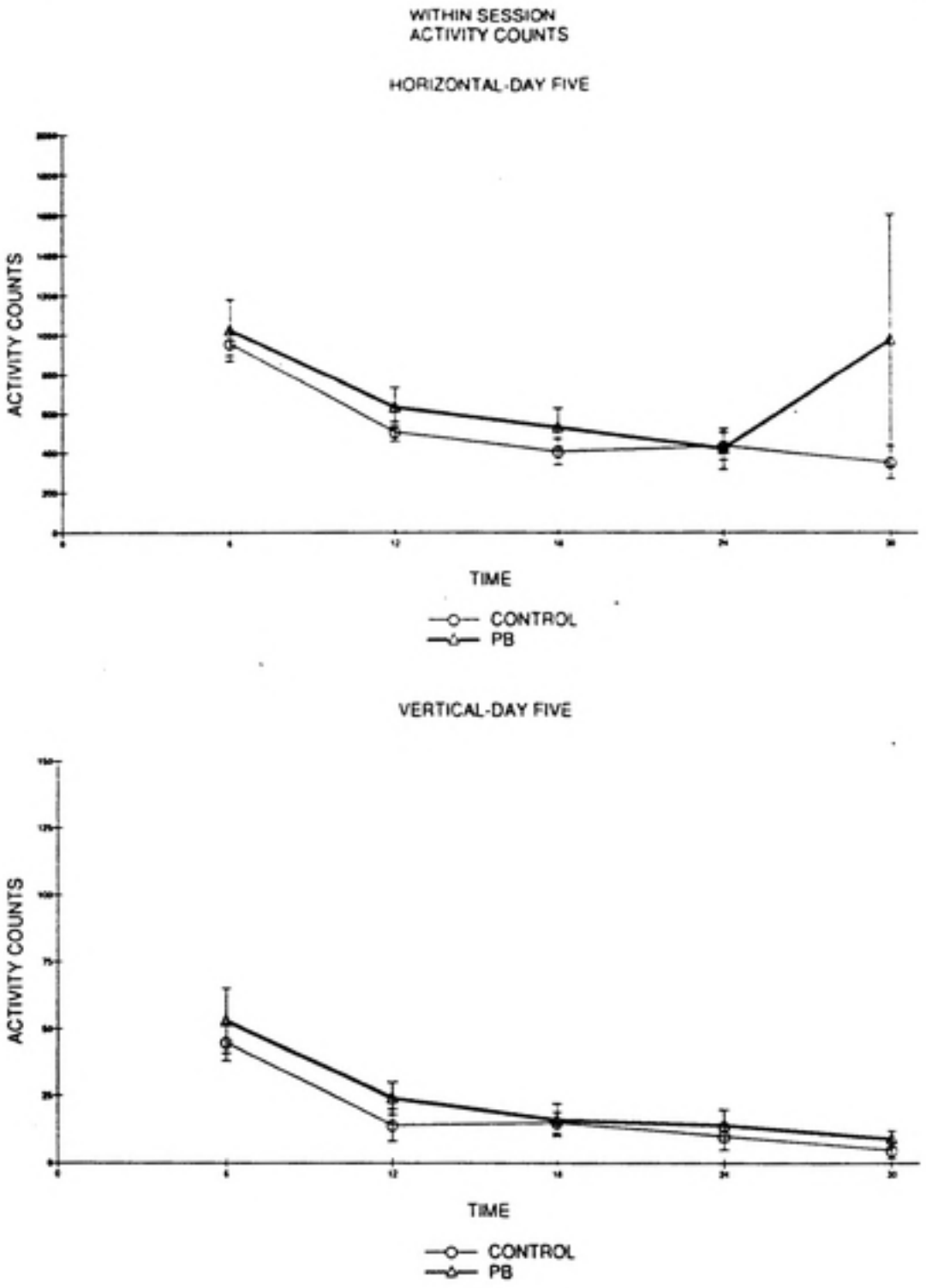

Fig. 14. Mean number of horizontal (top) and vertical (bottom) photocell counts in experiment 122 for Male Long Evans rats ingesting 0.2% lead acetate (N=8) or water (N=9) in five 6-minute intervals on day five of testing.

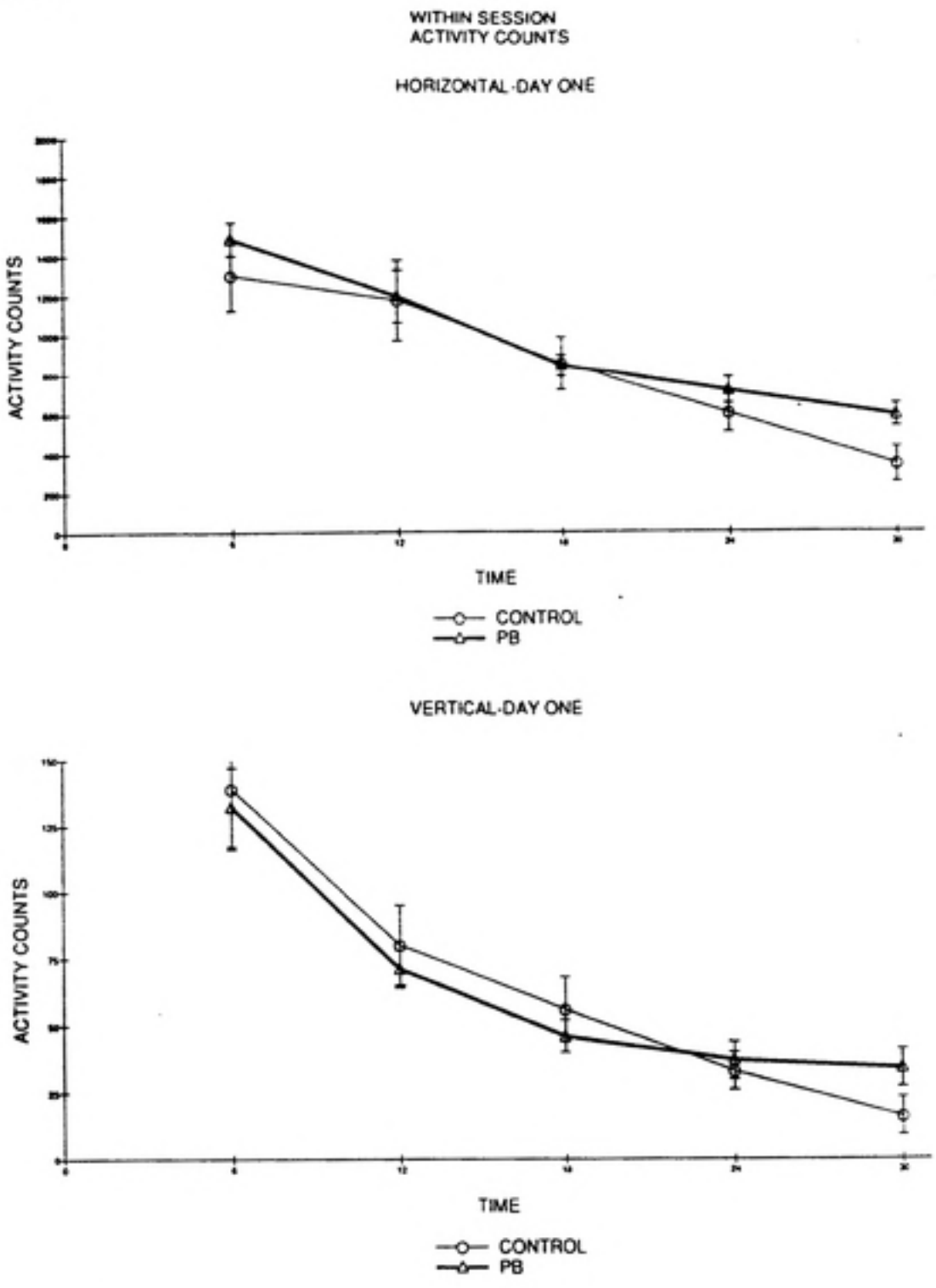

Fig. 15. Mean number of horizontal (top) and vertical (bottom) photocell counts in experiment 130 for Male Long Evans rats ingesting 0.2% lead acetate (N=12) or water (N=11) in five 6-minute intervals on day one of testing.

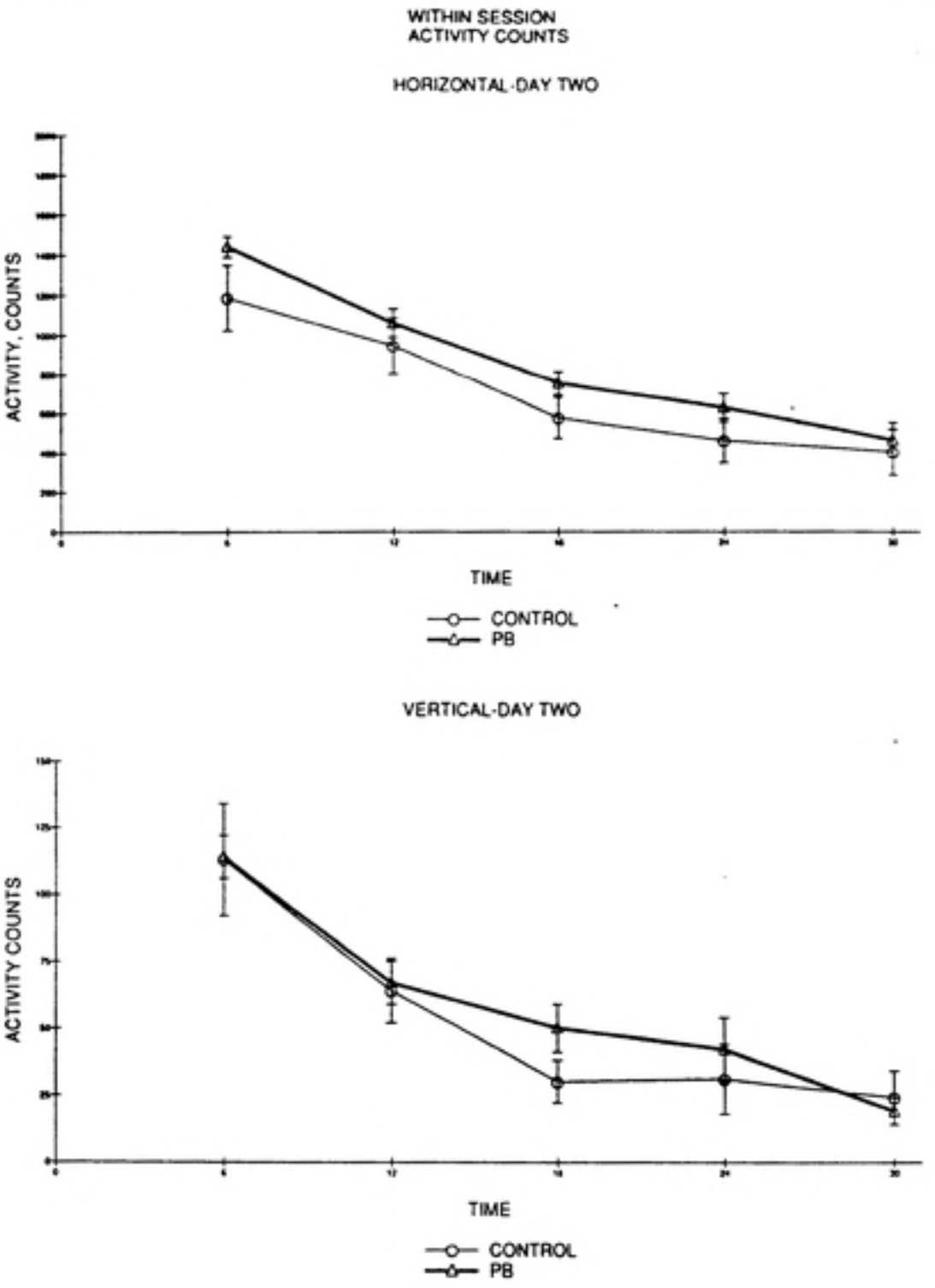

Fig. 16. Mean number of horizontal (top) and vertical (bottom) photocell counts in experiment 130 for Male Long Evans rats ingesting 0.2% lead acetate (N=12) or water (N=11) in five 6-minute intervals on day two of testing.

WS130

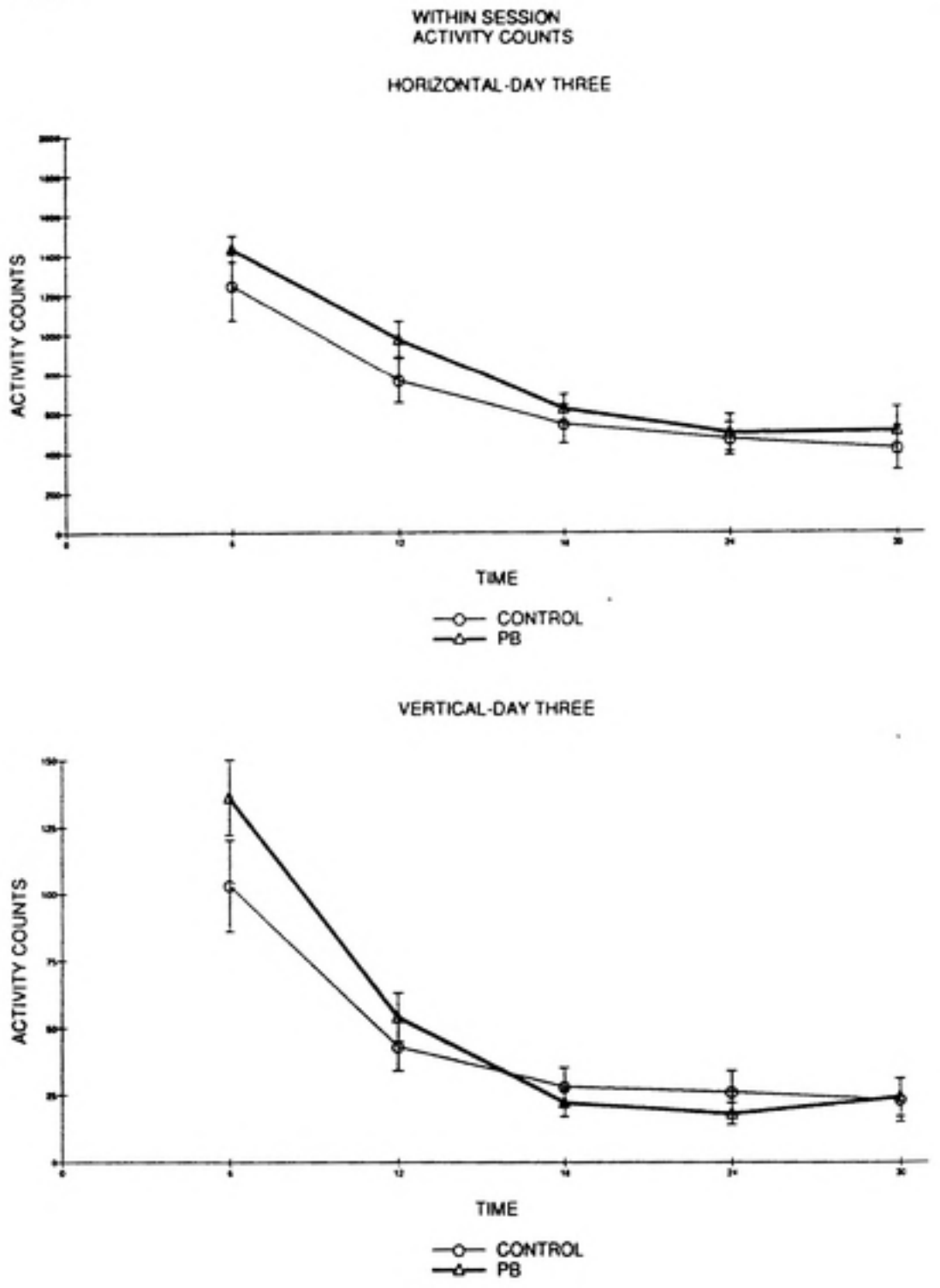

Fig. 17. Mean number of horizontal (top) and vertical (bottom) photocell counts in experiment 130 for Male Long Evans rats ingesting 0.2% lead acetate (N=12) or water (N=11) in five 6-minute intervals on day three of testing.

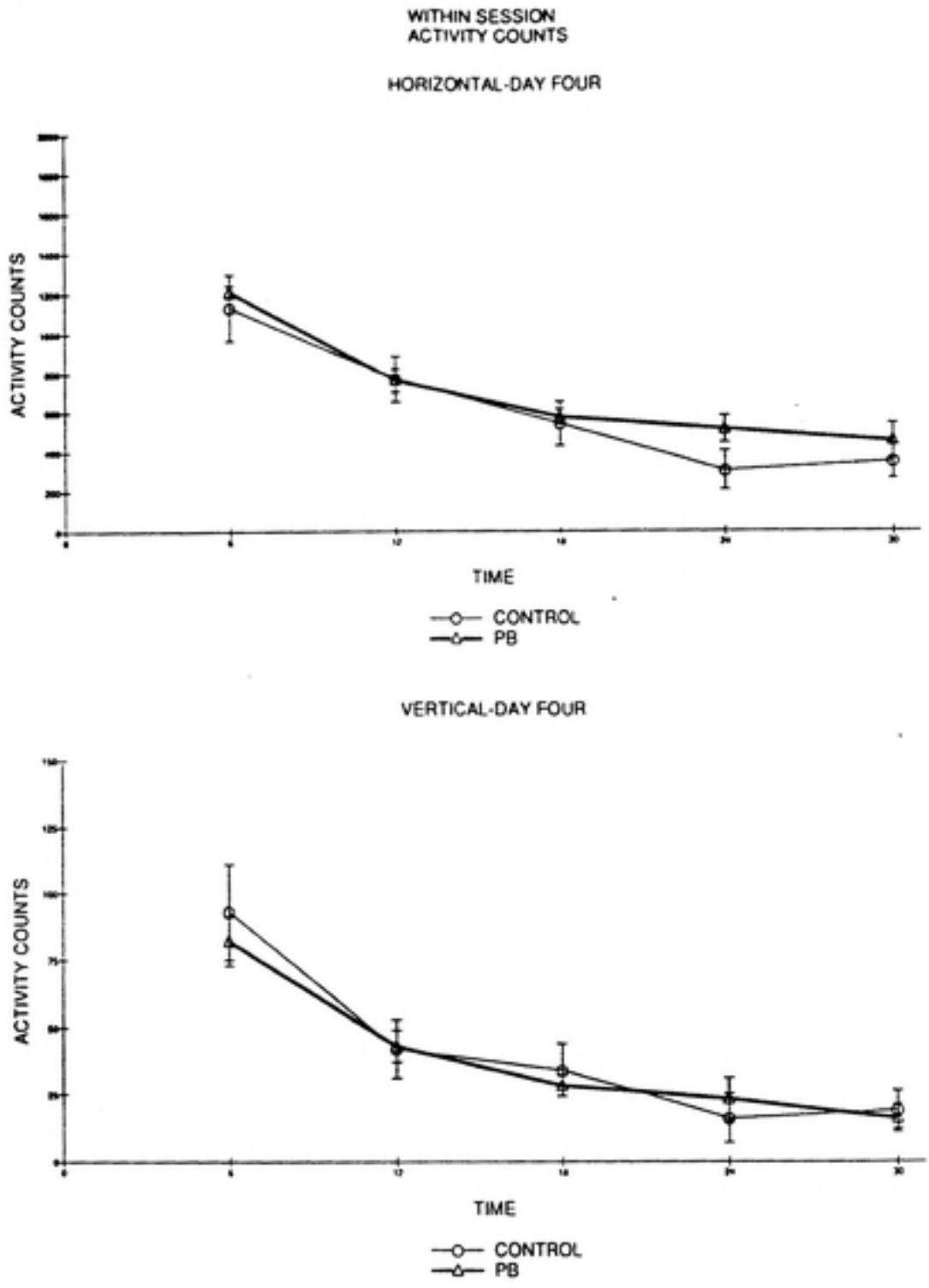

Fig. 18. Mean number of horizontal (top) and vertical (bottom) photocell counts in experiment 130 for Male Long Evans rats ingesting 0.2% lead acetate (N=12) or water (N=11) in five 6-minute intervals on day four of testing.

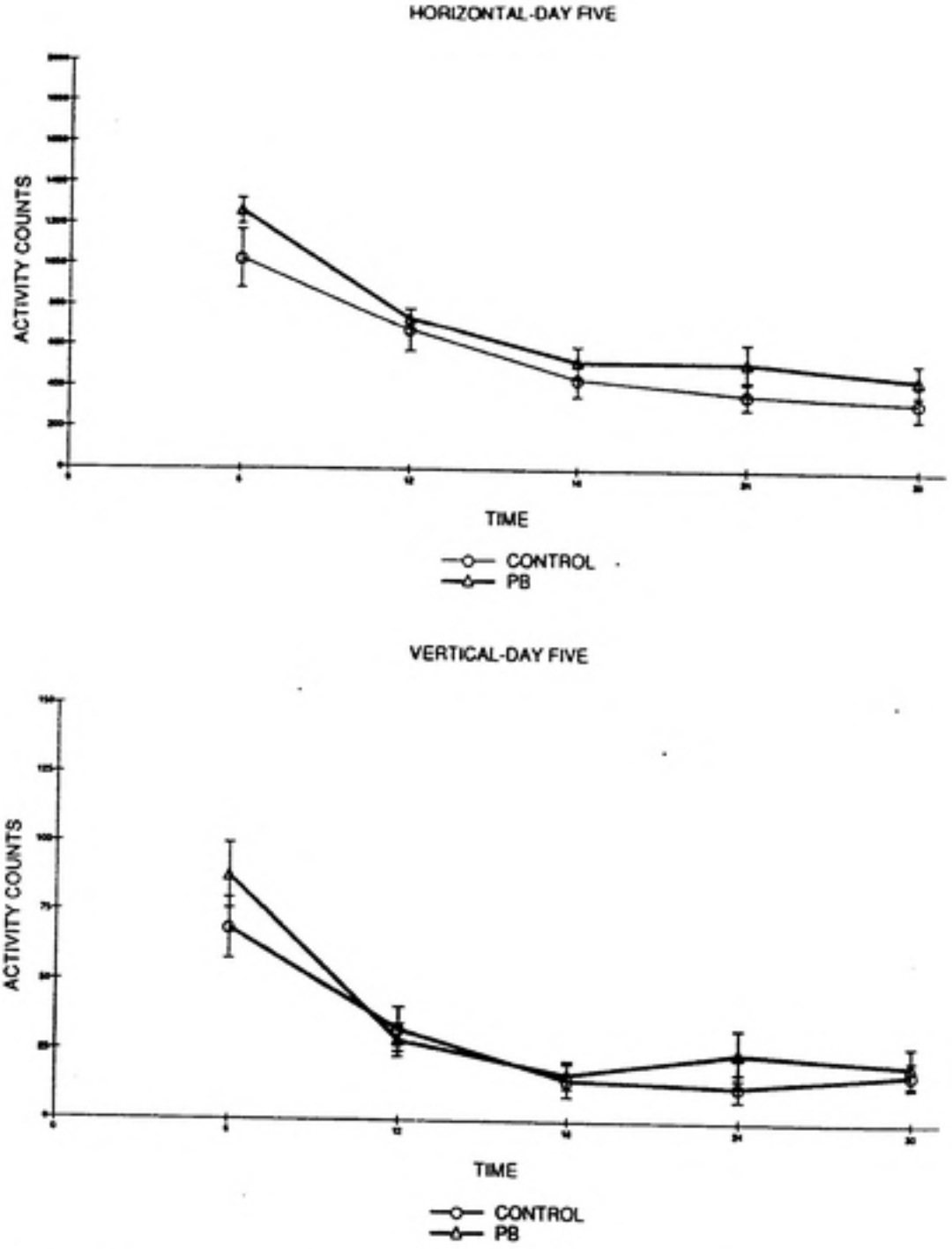

Fig. 19. Mean number of horizontal (top) and vertical (bottom) photocell counts in experiment 130 for Male Long Evans rats ingesting 0.2% lead acetate (N=12) or water (N=11) in five 6-minute intervals on day five of testing.

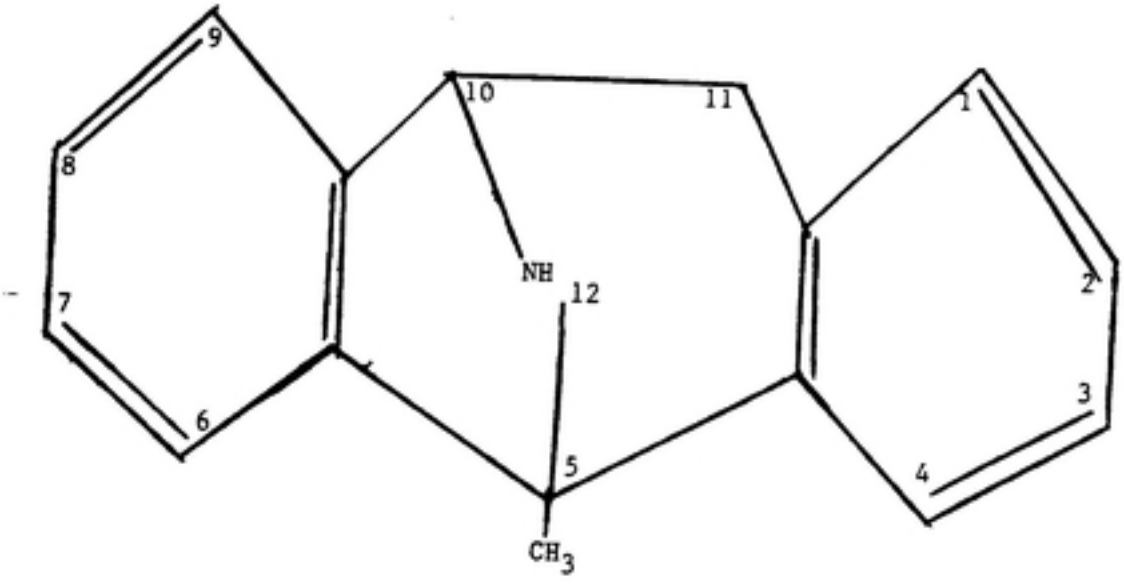

Fig. 20. Structure of MK-801. Metabolites: 12-OH, 2-OH, 8-OH; congeners: 5-ethyl, 3-bromo, 12-propyl

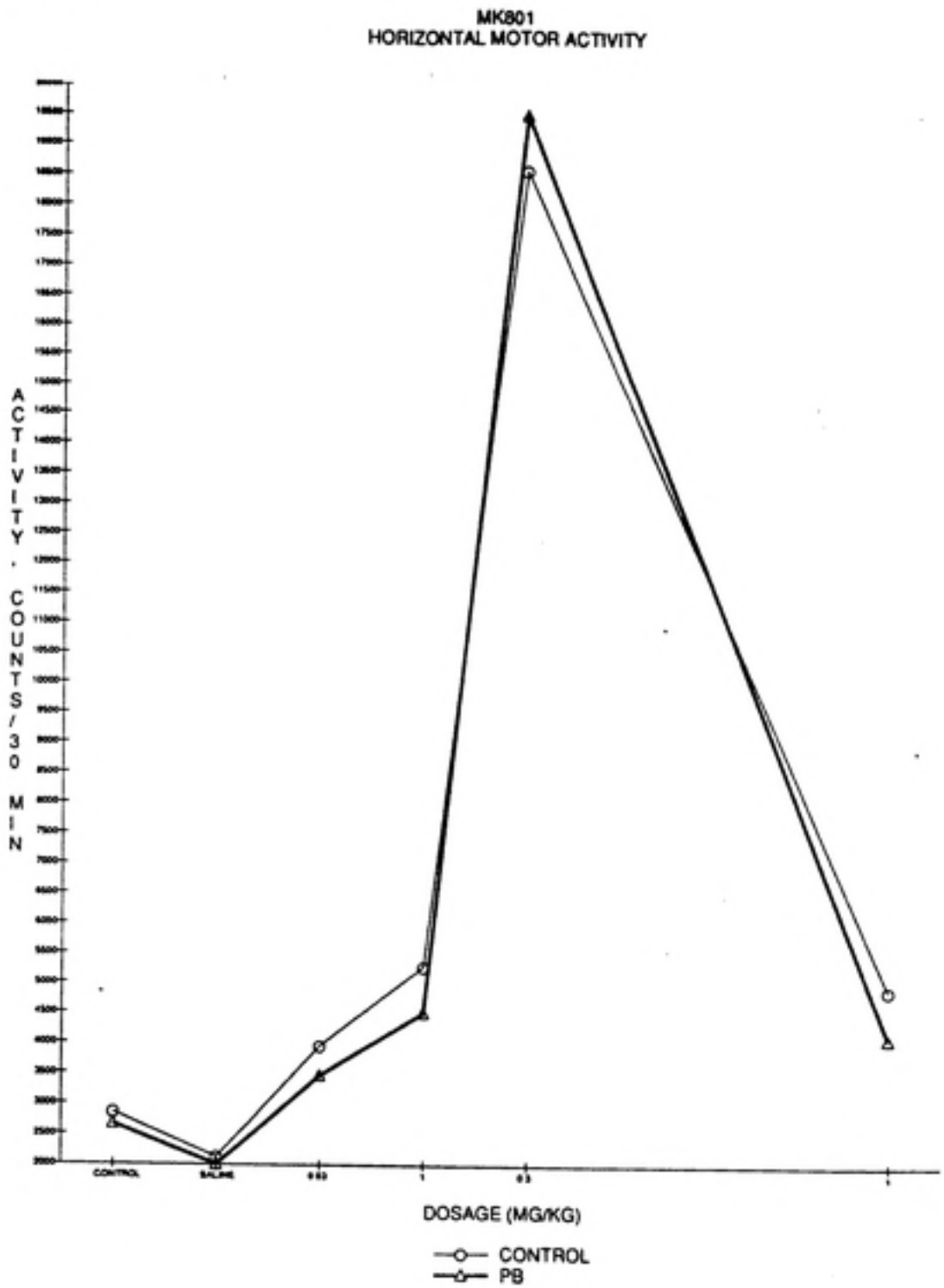

Fig. 21. Reproducibility of MK-801 effects on motor activity. Rats were treated with either a dosage of MK-801 or vehicle (0.0 mg/kg) and tested in the photocell activity chamber for 30 minutes beginning 30 minutes after treatment.

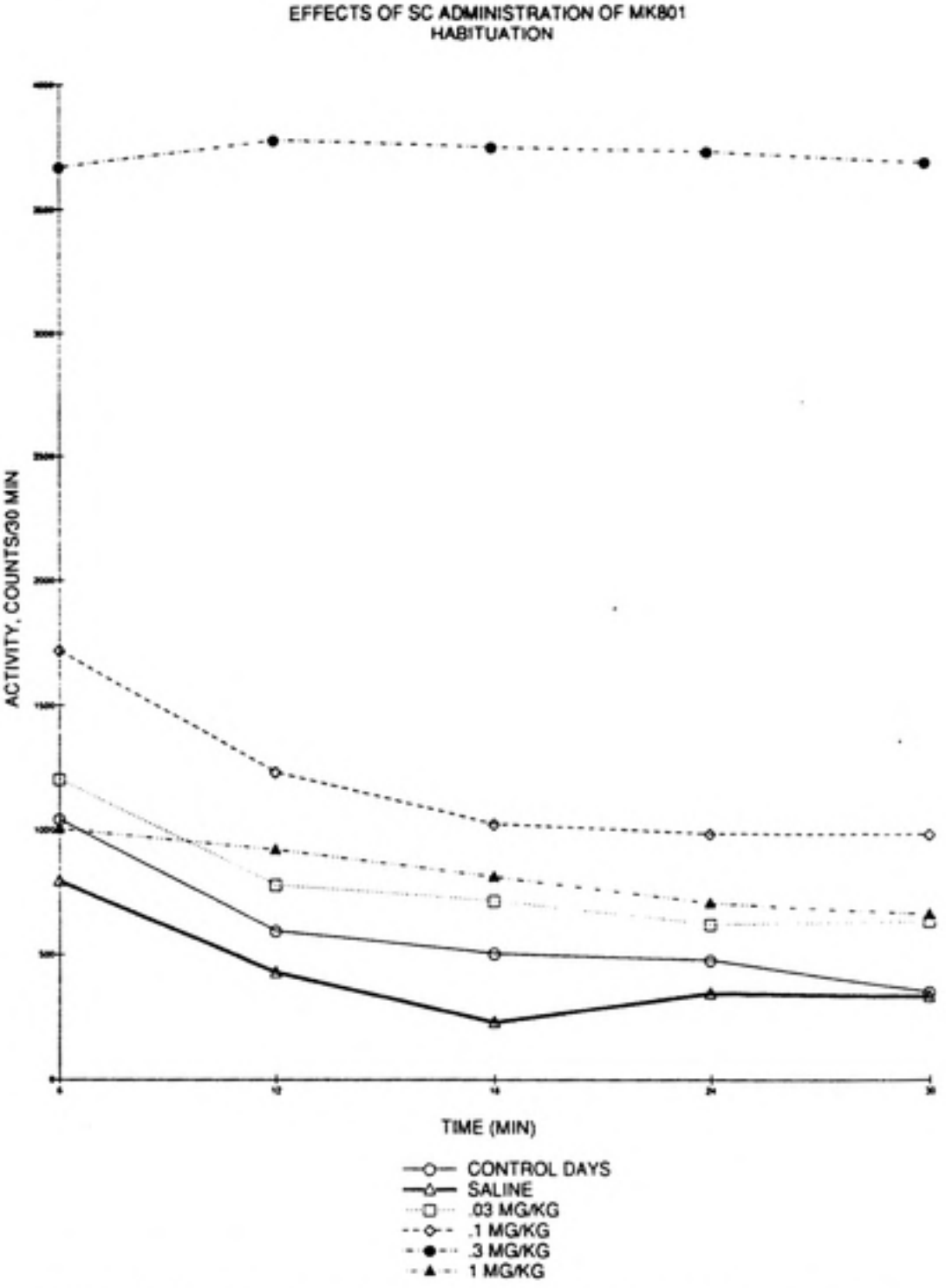

Fig. 22. Mean number of photocell counts for male Long Evans rats treated with either a dosage of MK-801 or vehicle (0.0 mg/kg) and tested in the photocell activity chamber for five 6-minute intervals beginning 30 minutes after treatment.

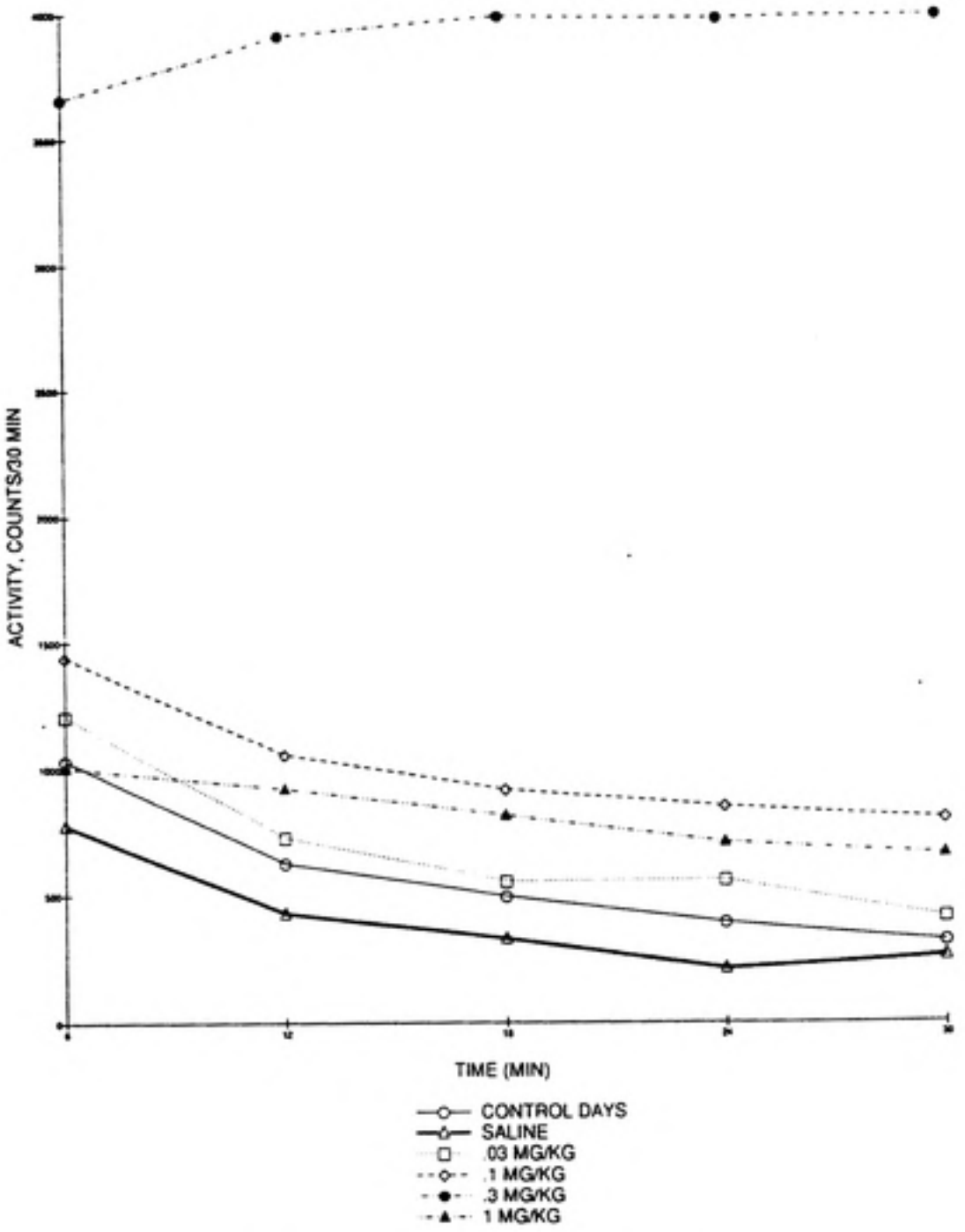

Fig. 23. Mean number of photocell counts for male Long Evans rats postnatally exposed to Pb and treated with either a dosage of MK-801 or vehicle (0.0 mg/kg) and tested in the photocell activity chamber for five 6-minute intervals beginning 30 minutes after treatment.

V. References

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