EPA-600/1-77-037
June 1977

Environmental Health Effects Research Series

STUDIES IN SUBCLINICAL LEAD EXPOSURE

Health Effects Research Laboratory
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

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June 1977

STUDIES IN SUBCLINICAL LEAD EXPOSURE

by

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Contract No. 68-02-1239

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U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF RESEARCH AND DEVELOPMENT
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FOREWORD

The many benefits of our modern, developing, industrial society are accompanied by certain hazards. Careful assessment of the relative risk of existing and new man-made environmental hazards is necessary for the establishment of sound regulatory policy. These regulations serve to enhance the quality of our environment in order to promote the public health and welfare and the productive capacity of our Nation's population.

The Health Effects Research Laboratory, Research Triangle Park, conducts a coordinated environmental health research program in toxicology, epidemiology, and clinical studies using human volunteer subjects. These studies address problems in air pollution, non-ionizing radiation, environmental carcinogenesis and the toxicology of pesticides as well as other chemical pollutants. The Laboratory develops and revises air quality criteria documents on pollutants for which national ambient air quality standards exist or are proposed, provides the data for registration of new pesticides or proposed suspension of those already in use, conducts research on hazardous and toxic materials, and is preparing the health basis for non-ionizing radiation standards. Direct support to the regulatory function of the Agency is provided in the form of expert testimony and preparation of affidavits as well as expert advice to the Administrator to assure the adequacy of health care and surveillance of persons having suffered imminent and substantial endangerment of their health.

One of the major pollutants of interest to the Health Effects Research Laboratory is lead. In particular, the health impact of low level lead exposure is of much current concern. This report covers the findings of an epidemiologic study of the neuropsychologic effects of low level lead toxicity. Evidence is presented suggesting that increased levels of lead in the body of children may result in decreased attention span and impaired perceptual motor function.

John H. Knelson, M.D.
Director,
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ABSTRACT

This study was initiated to examine the utility of neuropsychologic testing in identifying deficits in children with asymptomatic elevations in blood lead levels.

From the files of the Boston Lead Screening Project we selected black male children between the ages of six and eight years of age, considered asymptomatic for lead toxicity who had blood lead tests recorded between the ages of 1 1/2 and 5 years of age. High lead subjects were children with one or more blood lead levels greater than 50ug/dl. Low lead subjects were children with no blood lead level greater than 30ug/dl.

Forty-one high lead and 35 low lead subjects were tested by a battery of neuropsychologic tests measuring intelligence, verbal performance, visual motor performance, gross and fine motor function, and attention span. Other covariates measured were socioeconomic status, birthweight, and medical history. Seventeen high lead and 17 low lead subjects were excluded from data analysis because their medical history revealed either prematurity, significant head injury or other illness. The 24 high lead and 16 low lead males were similar with respect to age at time of testing, SES, and birthweight.

High lead children were consistently slower at each block of trials on the Reaction Time under Varying Conditions of Delay (a measure of attention), and performed significantly less well on Subtest I of the Frostig Battery. High lead subjects tended to perform less well on the Maze Coordination Test, and on the Tactile Form Recognition Test with the non-dominant hand.

CONTENTS

ACKNOWLEDGEMENTS

The generous cooperation of the Boston Lead Screening Project, directed by Mr. Ron Jones, and the Massachusetts Lead Poisoning Control Program, Dr. Robert Klein, Director, who made their files available to us, is gratefully acknowledged.

Mrs. Janice Adams was responsible for searching 20,000 subject cards in the Boston Lead Screening file, identifying, contacting and testing subjects, and played a major part in the data analysis. I wish to especially acknowledge her tireless and careful work.

Section 1

CONCLUSIONS & RECOMMENDATIONS

Black male children with blood lead levels measured at a mean age of 48 months greater than 50ug/100ml differed significantly from children similar with respect to sex, age, birthweight, and socioeconomic status but with a blood lead of 30ug/100ml on two neurobehavioral measures: reaction time under conditions of varying delay (a measure of attention) and Test I of the Frostig Battery (eye-hand coordination). High lead children also did less well on Maze Coordination, another measure of eye-hand coordination, and Tactile Form Recognition.

The sample size of this study and the small number of positive findings limits the ability to generalize from these results. The differences in eye-hand coordination and attention are in support of other studies of low level lead exposure in children (1,4,5,8,19,20). Future studies of larger numbers of children with low level lead exposure concentrating on indices of attention and eye-hand coordination are warranted.

Section 2

EXPERIMENTAL PROCEDURES

Study Sample

High Lead--

Black, male children, age 6-8 years, with blood lead levels > 50ug/100ml when screened between the ages of 1 1/2 to 5 years, but no history of lead encephalopathy.

Low Lead Controls--

Black, male children, age 6-8 years, with blood lead levels < 30ug/100ml when screened between the ages of 1 1/2 to 5 years.

All children were obtained from the register of the Boston Lead Screening Program, Boston City Hospital.

Subject Ascertainment

The Lead Poisoning Prevention Center made its files available to us on February 6, 1974.

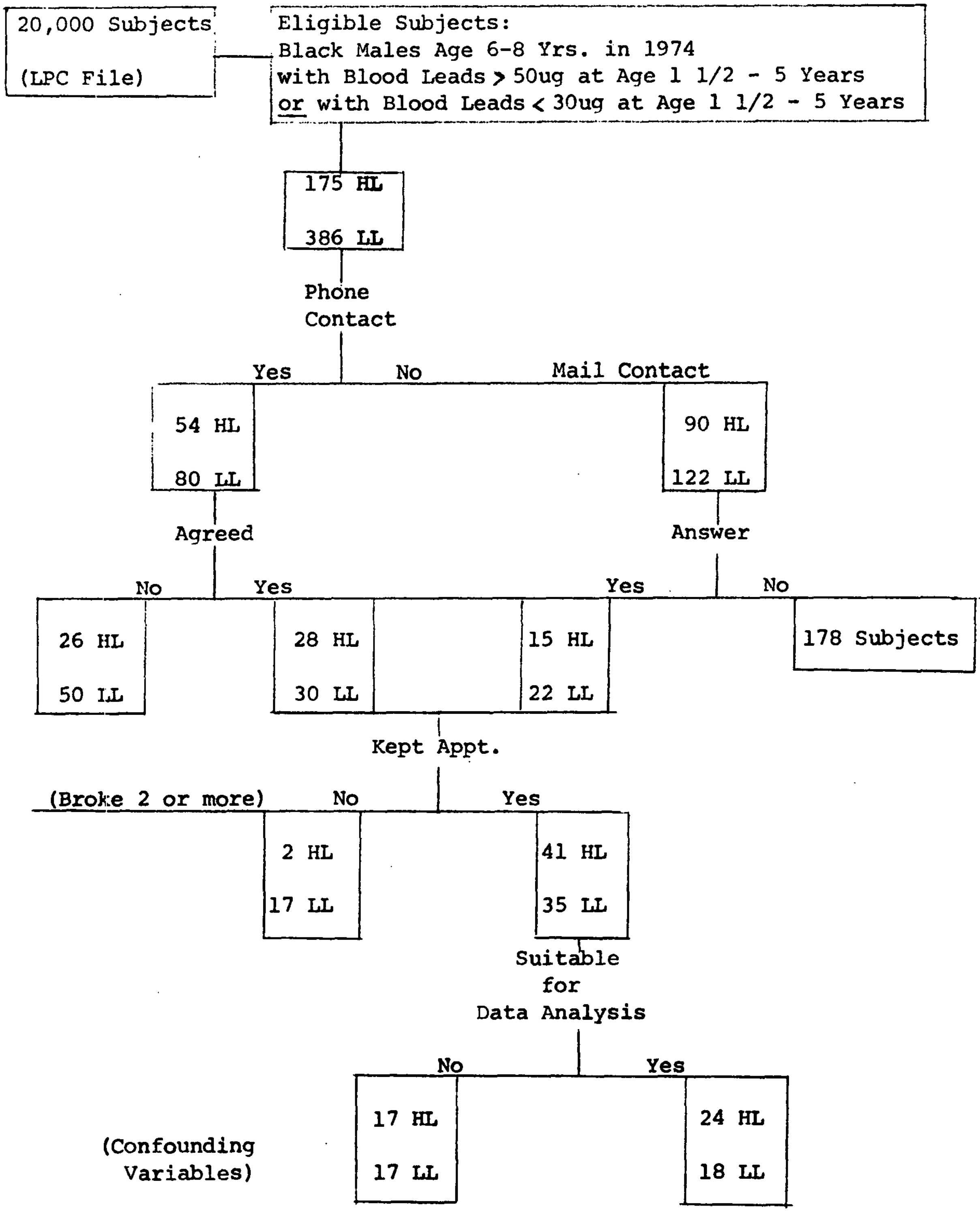
The files contained approximately 18,000 low lead (< 50ug/g) and 2,000 high lead (> 50ug/g) individuals. The following 10 months (February 1974 to September 1974) were spent extracting possible subjects, contacting them, and testing subjects. All 20,000 cards were individually checked. A total of 386 low lead subjects and 175 high lead subjects were identified. Subjects were tested from September 1973 to February 1975.

Contacting subjects was a major problem. Phones were not listed in the file for 79 controls and 41 high lead children (Figure I). Thirty percent of the control group and 38% of the high lead group whose phones were listed in the file had been changed to unpublished numbers. This in itself limited our population since in some cases it was the only way that race could be tactfully determined. We were finally able to reach 80 controls and 54 high lead subjects by phone. Nineteen percent of these controls and 22% of these high lead subjects refused to join the study. Thirty-eight percent of these controls and 52% of these high lead subjects accepted by phone.

A total of 212 (122 control and 90 high lead) first contact letters (see enclosure) with enclosed, self-addressed, stamped postcards were sent.

Figure I

Subject Ascertainment



Twenty-two controls and 15 high leads accepted by return card. Only one control and 4 high leads refused by return card. Follow-up letters were sent to non-respondants. Twenty-three percent of all letters were returned with no forwarding address. Subjects who cancelled their appointments more than twice were excluded.

From this total population we tested 35 control subjects and 41 high lead subjects. After testing, 17 high lead and 17 controls were excluded because of additional information the parents disclosed, such as prematurity, head injuries, or other confounding variables.

Outcome Data

Maternal History--

Each mother at the time the child received the neuropsychological profile, completed a health questionnaire (Appendix I).

Neuropsychological Battery--

Each child received the following neuropsychological battery:

Peabody Picture Vocabulary Test (14)--This test assesses vocabulary recognition by the use of pictures. Subject must choose one out of four pictures presented which best portrays the stimulus word. The stimulus words are arranged in order of increasing difficulty. Testing proceeds until six errors out of eight trials are obtained. Mental age, percentile score and IQ are computed from the raw score. Raw score = total answered minus number of errors.

Lincoln Oseretsky Motor Development Scale (15)--A shortened form employing 12 performances testing fine and gross motor function is employed. Each item is scored from 0 to 3, and a total score calculated.

Reaction Time under Varying Conditions of Delay (16)--This is a test of the ability to attend to a ready signal after varying periods of delay, and is one index of the subject's attention span. Subject is required to respond to an auditory stimulus by depressing a key after a ready signal is given. Four blocks of six trials each are given at 3, 12, 12, and 3 second ready periods. Means and standard deviations are calculated for each block.

Visual Motor Integration Test (12)--This is a test of perceptual function in which the subject must copy (with paper and pencil) geometric forms of increasing complexity. A mental age score is computed for each subject from standardized score sheets.

Frostig Developmental Test of Visual Perception (13)--This is a test of three operationally defined perceptual functions: (I) the ability to coordinate vision with hand movements; (IV) perception of an object in relation to the observer; (V) perception of the position of two or more objects in relation to each other.

I. Eye-Motor Coordination: Subject draws continuous straight, curved, or angled lines between boundaries of various width, or from point to point without guidelines.

IV. Position in Space: Subject makes discriminations of reversals and rotations of common objects presented in a series.

V. Spatial Relationships: Subject copies lines of various lengths and angles using dots as guide points.

A standard score for each subject is computed from raw scores.

Illinois Test of Psycholinguistic Abilities (17)--This is a test of communicative skills, measuring the capacity to receive, interpret, and transmit information through auditory, vocal, and visual motor channels.

1. Verbal Expression: Subject describes verbally four simple stimulus objects. Number and category of responses are coded.

2. Manual Expression: Subject demonstrates manually the use of a standard series of pictured objects. Number and category of responses are coded.

3. Auditory Closure: Examiner presents a series of words with certain sounds omitted. Subject must respond with the completed word.

4. Sound Blending: E presents successive sounds of words or nonsense words with a distinct break between the sounds. Subject is asked to verbalize the whole word.

Elements of the Halstead Reitan Battery (18)--Eleven items of this broad neuropsychologic assessment battery were selected which were not redundant to other tests in our profile, and which tested motor function, cerebral dominance, and haptic-kinesthetic performance.

1. Lateral Dominance: Subject is asked to perform 4 or 5 simple motor tasks. Dominance is determined.

2. Right-Left Discrimination: Subject is asked to discriminate right and left on himself and then on a cardboard figure of a child.

3. Finger Oscillation Test: Measures finger-tapping speed, using the index finger.

4. Tactile Performance Test: Blindfolded the subject is asked to fit wooden blocks into their proper spaces on the formboard provided, with dominant hand, non-dominant hand, and then both hands. S is asked to recall shapes and location of blocks.

5. Tactile Form Recognition: S is asked to identify the shape (circle, square, triangle, cross) of a small plastic chip without seeing it.

6. Tactile Finger Recognition: S must identify individual fingers after tactile stimulation without the use of vision.

7. Fingertip Writing Perception: S must report without the use of vision whether an X or an O was written on his fingertip.

8. Maze Coordination: S is required to move a stylus through a vertical maze without touching the sides. Number of touches and total time against the side is recorded electronically.

9. Groove Steadiness: S must move a stylus up and down a vertical groove without touching the sides. Number and time of touches is recorded.

10. Steadiness Test: S must hold a stylus in a hole without touching the sides. Four successively smaller holes at 15 seconds per hole. Number and time of touches is recorded.

11. Grooved Pegboard: S must put small metals pegs into a pegboard as fast as he can. Each peg is keyed so that its orientation must be precisely adjusted in order to be inserted.

Raw scores for each subtest were computed.

Section 3

RESULTS AND DISCUSSION

Data Analysis

Because of the small sample size and because the outcome measures did not appear to be normally distributed, non-parametric tests of ranks (Mann Whitney-U) were applied to the psychological data. One tailed test of significance was chosen because the direction of effect was expected to favor low lead subjects.

All children included in the analysis (24 high leads and 18 controls) were Black males. The two groups were similar with respect to age at time of testing, socioeconomic status, and birthweight.

	Mean Age at Testing	Mean Socioeconomic Status*	Mean Birthweight
High Lead	78.6±6.4	4.4±.6	3.44±.46kg
Low Lead	79.9±6.8	4.6±.5	3.37±.43kg

*Hollingshead's Two Factor Index of Social Position

No significant differences were found between high and low lead groups on the Visual Motor Integration Test, Frostig subtests IV and V, Peabody Picture Vocabulary Test, Illinois Test of Psycholinguistic Abilities, and subtests of the Halstead Reitan Battery (Tables I-IV).

High lead children did significantly poorer on subtest I of the Frostig Battery, a test which measures eye-hand coordination.

High lead children were consistently slower to respond to the onset stimulus on the reaction time test in each block of trials (Table II). The differences were most marked in blocks 3 and 4, but only reached significance in block 4 (3 second delay). This is consistent with the hypothesis that the children were unable to attend closely to the stimulus under conditions of longer delay, or after 10 minutes at a boring task.

High lead children did less well at the Maze Coordination Test, but this difference did not reach significance. They also tended to perform less well with the non-dominant hand on Tactile Form Recognition.

TABLE I

Neuropsychological Outcome Measures in High and Low Lead Children

Test		N	Median Score	Range	U	z	p	Remarks
Visual Motor Integration	HL	23	-13.5	34	209	0.71	.24	Units are difference in months between achieved and standard score.
	LL	16	-14.5	32				
Frostig								
I	HL	23	8.8	7	109	-1.90	.03	Units are scale scores.
	LL	15	10.5	8				
IV	HL	23	9.9	8	196	0.72	NS	
	LL	15	9.3	7				
V	HL	23	9.1	5	170	-0.07	NS	
	LL	15	9.0	8				
Peabody Picture Vocab.	HL	24	53.0	96	183	-0.25	NS	Units are percentiles.
	LL	16	59.5	86				
Lincoln-Oseretsky	HL	22	38.5	30	200	0.71	NS	Units are raw scores.
	LL	16	38.5	23				

(One-tailed test of significance)

TABLE II

Neuropsychological Outcome Measures in High and Low Lead Children

Test		N	Median Score	Range	U	z	p	Remarks
Reaction Time								
Block 1 (3 sec. delay)	HL	22	363	660	181.0	0.49	NS	Score is in milliseconds.
	LL	15	340	340				
Block 2 (12 sec. delay)	HL	22	475	640	159.5	-0.19	NS	
	LL	15	450	500				
Block 3 (12 sec. delay)	HL	19	570	650	149.0	0.58	NS	
	LL	14	495	360				
Block 4 (3 sec. delay)	HL	18	460	430	174.0	1.82	.03	
	LL	14	385	230				
Illinois Test of Psycholinguistic Abilities								
Verbal	HL	23	38	29	154.0	-0.22	NS	Units are scale scores.
	LL	14	37	21				
Manual	HL	23	42.5	28	222.0	1.08	NS	
	LL	16	38.5	20				
Auditory Closure	HL	22	35.5	17	177.0	1.16	NS	
	LL	13	32.8	11				
Sound Blending	HL	22	43.5	33	176.0	1.13	NS	
	LL	13	37.5	32				

TABLE III

Neuropsychological Outcome Measures in High and Low Lead Children

Test		N	Median Score	Range	U	z	p	Remarks
Finger Tapping								
Dominant Hand	HL	23	41.6	22	127.5	-0.36	NS	Units are mean # of taps - 5 trials of 10 sec. each.
	LL	12	41.0	13				
Non-Dominant	HL	23	35.6	24	157.0	0.66	NS	
	LL	12	34.5	18				
Tactile Performance	HL	12	-163.0	1173	44.0	0.18	NS	Units are deviation in seconds from standard score.
	LL	7	-164.0	554				
Tactile Form Recognition								
Dominant	HL	23	25.5	21	165.0	-0.54	NS	Units are in seconds sum of 2 trials/hand
	LL	16	25.6	18				
Non-Dominant	HL	23	23.5	18	134.0	-1.43	NS	
	LL	16	23.5	17			.07	
Fingertip Writing								
Dominant	HL	23	9.77	3	209.0	0.71	NS	Units are # of correct choices.
	LL	16	9.61	5				
Non-Dominant	HL	23	9.90	5	197.0	0.37	NS	
	LL	16	9.83	5				
Tactile Finger Recognition								
Dominant Hand	HL	23	7.36	8	182.0	-0.06	NS	Units are # of correct choices.
	LL	16	7.25	7				
Non-Dominant	HL	23	6.38	8	165.0	-0.54	NS	
	LL	16	6.90	8				

TABLE IV

Neuropsychological Outcome Measures in High and Low Lead Children

Test		N	Median Score	Range	U	z	p	Remarks
Maze Coordination								
Dominant Hand	HL	23	16.0	29	228.0	1.27	NS	Units are time in seconds touching side of maze, sum of 2 trials/ hand.
	LL	16	12.5	34				
Non-Dominant	HL	22	22.5	28	160.5	-0.46	NS	
	LL	16	23.0	24				
Groove Steadiness								
Dominant Hand	HL	23	10.5	30	215.0	0.90	NS	Units are time in seconds touching side of groove, sum of 2 trials/hand.
	LL	16	8.5	23				
Non-Dominant	HL	23	12.5	32	172.0	-0.34	NS	
	LL	16	13.0	27				
Motor Steadiness								
Dominant Hand	HL	23	13.1	29	174.0	-0.29	NS	Units are time in seconds touching edge of holes, sum of 1 trial on each of 4 holes/hand.
	LL	16	11.0	41				
Non-Dominant	HL	23	18.0	24	207.0	0.66	NS	
	LL	16	19.0	29				
Grooved Pegboard	HL	22	40.1	28	150.0	-0.77	NS	Units are time in seconds to completion.
	LL	16	41.5	42				

Discussion

Impaired function in children with past elevations of blood lead levels, but no history of encephalopathy was found in two areas: eye-hand coordination (Frostig I), and attention as measured by reaction time under conditions of varied delay. Suggestive, but not statistically different, differences were also found in Maze Coordination (another measure of eye-hand coordination) and Tactile Form Recognition with the non-dominant hand.

On a large number of other tests of fine and gross motor function, language processing ability, and cognition we failed to find significant differences. It is possible that low level lead exposure does not affect performance in these areas. On the other hand, it is possible that lead effects could have been overlooked because the sample size may have been too small to detect subtle differences in exposure, or that the tests employed were insensitive to small lead effects. Because a large number of tests were applied, and a small number of significant differences between high and low lead subjects observed, the interpretation of the positive differences must be drawn with caution.

The identification of early lead exposure by blood lead determination has certain well-recognized methodologic difficulties inherent in its use. In this study we were compelled to rely upon blood lead data obtained in a large public health screening program. In some cases only one sample per child was obtained. The bloods were drawn at approximately 48 months of age, about one year past the time when the incidence of pica begins to decline. The blood lead levels may be considered an estimate of exposure, but it is possible that some of our controls had higher levels earlier in their lives.

The difficulties in eye-hand coordination and attention are consistent with the earliest report of late effects of lead exposure by Byers and Lord (1) who reported sensorimotor defects, impulsivity and short attention span as prominent sequelae. Bradley and Baumgartner (19) and Mellins and Jenkins (20) also found that children who recovered from lead intoxication had impaired perceptual motor function when later studied.

Children with "asymptomatic" increases in body lead burden have also been reported to perform less adequately in these areas by Perino and Ernhart (4) (perceptual items of McCarthy Scale), Burde and Choate (5) (fine motor performance on Binet Scale), and Landrigan et al, (8) (performance items of Wechsler Scale).

The differences in attention found may bear on clinical observations reported. Children who recover from plumbism are frequently hyperactive (1). David (6) has reported that hyperactive children with no history of antecedent risk factors have higher mean blood lead levels, and when chelated, excrete more lead in their urine. Silbergeld and Goldberg (21), Michaelson and Sauerhoff (22) have produced hyperactivity in suckling rats given lead in mother's milk. This paradigm (reaction time under conditions of varying delay) has been shown to discriminate between children with learning disabilities and controls matched on I.Q., and appears to be a sensitive method of scaling one function of attentional performance.

While the difference between the high lead and control children reached statistical significance only in the fourth block of trials, the high lead children performed less well in each block. Further study of a larger sample of subjects is indicated.

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Appendix I

Parent Questionnaire

Child's Name ______________________ Mother's Name ______________________
Last First Last First

Birthdate _____ ____ ____ Race (specify): Caucasian____
Month Day Year Black _____
Other _____
Grade _____ (Specify)

Child's Birthplace ______________________________

Length of Pregnancy: Early____ 9 mos._____ Late_____

How early_____ How late _____

Birthweight _____lbs. _____oz.

Complications: Yes _____ Specify: ______________________________
No_____
____

Child left hospital with
mother: Yes _____
No_____ If no, why: ______________________________
____

Illness:
Head Injury: Yes_____ No_____ Other problems (explain): ____________

Hospitalizations: Yes____ No___ ______________________________

If yes, explain: ______________________________

Seizures: Yes _____ No_____

Immunizations:

Smallpox: Yes_____ No_____
Diptheria: Yes_____ No_____
Polio: Yes_____ No_____
Oral_____
Shots_____
Measles: Yes_____ No_____

Has your child ever experienced:

Pica (eating of non-food substances)____
Abdominal Colic_____
Clumsiness_____
Irritability_____

Parent's Picture of Child

Is he/she active: No_____ Yes_____ Overactive_____

Is his/her general health good: No_____ Yes_____

School Adjustment:

Has teacher called you in other than for routine talks? No_____ Yes_____
Any failed grades? No_____ Yes_____
Special problems? No_____ Yes_____
Are your child's marks generally: Poor_____
Good_____
Very good_____

General Adjustment	No	Yes
Is your child generally happy?	____	____
Does he or she fight excessively?	____	____
Can your child stick to one task?	____	____
Sit quietly when asked?	____	____
Ignore distractions?	____	____
Does your child get along with friends?	____	____
Is he/she a loner?	____	____

Parent Data

Mother's age at date of child's birth: _______years

Marital status: Married _____ Separated _____ Divorced_____ Widowed _____

Never married _____

Father's occupation__________________________ Education 0 1-6 7 8 9 10 11 12 college____

Mother's occupation __________________________Education 0 1-6 7 8 9 10 11 12 college ____

The Children's Hospital Medical Center

300 Longwood Avenue, Boston, Massachusetts 02115, Telephone: (617) 734-6000

Dear Mrs.

We are conducting a study of child development in relation to exposure to lead. The children we are studying were tested for lead when they were five years old or younger, and are now between six and eight years of age. Your child is eligible for the study.

The children in the study will receive tests of motor coordination, sensory ability, and problem solving. There will be no blood tests. Many children have found the tests an interesting and pleasant challenge. There will be only one testing session which will occupy about 2 1/2 to 3 hours. As a stipend, each family will receive $10.00 plus transportation expenses.

This is an important study in which you can make a contribution to the understanding of what helps children to develop fully. We hope you will choose to participate by filling out the enclosed card. We will then make an appointment at your convenience.

If you have any questions, please do not hesitate to contact us at 734-6000, extension 3400.

Sincerely,

Herbert L. Needleman, M.D.

Enclosure

TECHNICAL REPORT DATA

(Please read Instructions on the reverse before completing)

1. REPORT NO. EPA-600/1-77-037	2.	3. RECIPIENT'S ACCESSION NO.
4. TITLE AND SUBTITLE Studies in Subclinical Lead Exposure		5. REPORT DATE June 1977
		6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S) Herbert L. Needleman, M.D.		8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS The Children's Hospital Medical Center 300 Longwood Ave. Boston, MA 02115		10. PROGRAM ELEMENT NO. 1AA601
		11. CONTRACT/GRANT NO. 68-02-1239
12. SPONSORING AGENCY NAME AND ADDRESS Health Effects Research Laboratory RTP,NC Office of Research and Development U.S. Environmental Protection Agency Research Triangle Park, N.C. 27711		13. TYPE OF REPORT AND PERIOD COVERED
		14. SPONSORING AGENCY CODE EPA 600/11
15. SUPPLEMENTARY NOTES		

16. ABSTRACT

This study was initiated to examine the utility of neuropsychologic testing in identifying deficits in children with asymptomatic elevations in blood lead levels.

From the files of the Boston Lead Screening Project we selected black male children between the ages of six and eight years of age, considered symptomatic for lead toxicity who had blood lead tests recorded between the ages of 1-1/2 and 5 years of age. High lead subjects were children with one or more blood lead levels greater than 50ug/dl. Low lead subjects were children with no blood lead level greater than 30ug/dl. Subjects were tested by a battery of neuropsychologic tests measuring intelligence, verbal performance, visual motor performance, gross and fine motor function, and attention span. Other covariates measured were socioeconomic status, birthweight, and medical history. High lead children were consistently slower at each block of trials on the Reaction Time under Varying Conditions of Delay (a measure of attention), and performed significantly less well on Subtest I of the Frostig Battery. High lead subjects tended to perform less well on the Maze Coordination Test, and on the Tactile Form Recognition Test with the non-dominant hand.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
lead toxicity biological surveys demographic surveys sociopsychological surveys children		06 T

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