U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
CENTER FOR DISEASE CONTROL
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH
CINCINNATI, OHIO 45226

HHE 76-36-369
SUPPLEMENTAL REPORT
(FOLLOW UP MEDICAL STUDY TO HHE 76-36-339)

EAGLE PICHER INDUSTRIES, INC.
JOPLIN, MISSOURI

MARCH 1977

FOLLOW UP OF HEALTH HAZARD EVALUATION (76-36-339)

BACKGROUND:

During a NIOSH Health Hazard Evaluation (76-36-339) of lead exposure at the Eagle Picher Industries, Lead Chemicals Plant in Joplin, Missouri, 17 of 53 workers examined were found to have elevated blood urea nitrogen (BUN) levels on at least one of two determinations; two workers had borderline results. Levels ranged from 21 to 44 mg/100ml. Ten of these workers had been treated with oral calcium disodium EDTA on at least one occasion. Symptoms and signs of lead toxicity in this group included peripheral neuropathy, anemia, and gastrointestinal and neuromuscular symptoms. Serum creatinine levels were within normal limits on all workers tested.

Since elevated BUN levels are associated with renal disease, a well-recognized sequela of chronic lead exposure, further medical evaluations were deemed necessary to determine:

1) the extent of renal functional impairment in these workers;
2) the role of occupational lead exposure in the etiology of this disease.

Accordingly, these 19 workers (two workers with borderline results were included) were referred to a board-certified nephrologist in Tulsa, Oklahoma for outpatient diagnostic studies which were performed in July, 1976.

METHODS:

Following complete history and physical examination, blood and urine tests were performed on specimens from each worker. In evaluating renal concentrating ability, the osmolality of a urine sample collected after a 12-hour water fast was determined.[1] Creatinine and lead clearances were determined using one hour timed urine collections and simultaneously collected blood samples. Lead levels were determined by atomic absorption spectrophotometry. $Beta_2$microglobulin levels were determined using a radioimmunoassay procedure.* Urinary amino acid screen was performed using thin layer chromatography.

*Kits produced by Pharmacia Diagnostics, Inc., Upsala, Sweden.

Urine animolevulinic acid (ALA) was measured by standard techniques. Blood chemistry tests (including creatinine, BUN, and uric acid) were performed using an automated clinical analyzer. Hemogram, differential, routine urinalysis, and VDRL were performed by standard methods.

Participants were informed prior to testing of the voluntary nature of the studies and that medical information would be treated in a confidential manner in compliance with the provisions of the Privacy Act.

RESULTS:

History: Six of the 19 workers were hypertensive (blood pressure greater than 140/90 by history or when examined during this evaluation). Two workers were on treatment for hypertension at the time of examination. One hypertensive worker gave a history of a cerebrovascular accident in 1975. Eleven workers reported histories of musculoskeletal symptoms (wrist, elbow, back, or shoulders). Three men complained of recurrent abdominal colic and two men noted chronic easy fatiguability.

PHYSICAL EXAMINATION

Physical examinations were generally within normal limits. No wrist drop or lead lines were noted.

LABORATORY EXAMINATIONS:

1. Renal Function Testing

Five of the 19 workers tested had elevated BUN levels (>22 mg/100ml) and one had an elevated serum creatinine concentration (>1.5 mg/100ml) (Table 1). However, 8 (42%) had decreased creatinine clearance (<91 ml/min/1.73 sq m BSA) (Table 2). Impaired urine concentrating ability (i.e., inability to concentrate the urine above 800 mosm/liter after an overnight water fast) was noted in 8 of 15 workers tested (Table 2).

Lead clearance, calculated by the standard formula*[1], tended to decrease with the increasing duration of exposure to lead (Figure 1). This inability to clear lead was independent of the age of the worker: analysis of data from 45-55 year old men shows the same negative relationship between duration of exposure and clearance rate (Figure 2).

Routine urinalysis were essentially within normal limits.

*$C = \frac{UV}{P}$ where C = clearance; U = urine lead concentration; P = blood lead concentration; V = urine flow rate over collection period

LEAD TESTS:

Fifteen (79%) workers had blood lead levels >60 ug/100ml, 7 (37%) had levels >80 ug/100ml. Erythrocyte protoporphyrin (EP) and urinary ALA levels showed comparable elevations (Table 3). EP and ALA-U levels were not correlated with lead clearance rate (r = .05 and .17 respectively).

HEMATOLOGIC TESTS:

Five workers were anemic (hemoglobin less than 14 gm/100ml) (Table 3). Hemoglobin levels were not correlated with blood lead or EP levels or with lead clearance rate.

OTHER TESTS:

Serum chemistry tests were generally within normal limits. Urinary $beta_2$ microglobulin levels were strikingly elevated in two workers (993 and 4890 ug/liter) and normal in all other tested. Urinary amino acid screen was normal in all.

DISCUSSION:

These studies clearly demonstrate a significantly increased prevalence of mildly to moderately severe kidney disease in employees at the Eagle Picher plant in Joplin, Missouri. Although further studies are needed to clarify the cause of these disorders, lead nephropathy is a likely etiology for several reasons. These workers have been heavily exposed to lead for prolonged periods (5-30 years) and manifest other toxic sequelae of lead exposure including anemia, recurrent colic and joint symptoms. Both renal glomerular and tubular dysfunction were noted in these men, a pattern previously noted[2,3] in other studies of lead nephropathy. A positive relationship exists between the degree of renal dysfunction (impaired lead clearance) and duration of exposure to lead; an effect which is independent of age. In view of these findings, other etiologies of renal disease seem unlikely but must be ruled out with further testing.

This study illustrates the insensitivity of blood urea nitrogen and serum creatinine determinations and routine urinalysis in detecting renal disease; this finding has been well documented in the medical literature.[1] More sensitive measures should be used in screening for lead nephropathy in exposed populations; such tests could include measurement of lead clearance, creatinine clearance, and urine concentrating ability as were done in the current report. All testing was performed over several hours in a doctor's office and could be adapted to in-plant screening.

In view of the impaired lead clearance noted in some of these workers, they might be expected to demonstrate greater toxicity from lead exposure than coworkers without such impairment. However, we did not find any relationship between hematologic toxicity and impaired renal function. Of greater importance is the potentiation of lead neurotoxocity by lead nephropathy which has been previously reported but was not evaluated in this study. Further work is indicated to clarify the significance of impaired lead clearance ability. The current report of mildly to moderately severe renal disease which may relate to lead exposure at Eagle Picher Industries, Lead Chemicals Plant in Joplin, Missouri, further illustrates the importance of reducing lead exposure at this plant. The recommendations made in the previous HHE report should receive further attention as well as those noted below.

RECOMMENDATIONS:

1) Seven workers identified by the nephrologist (Dr. Browning) as having impaired renal function should be removed from lead exposure. These individuals should be reassigned by the company to a lead free area of employment. Any lead exposure, even at air levels below the OSHA standards, may exacerbate existing renal disease. This recommendation applies even to individuals with renal impairment which is felt to be unrelated to lead exposure.

2) Further medical studies are indicated to determine the etiology and reversibility of renal functional impairment. These studies should be performed as soon as possible to avoid further deterioration in renal function. NIOSH will pay for the medical expenses of those wishing to have further tests.

3) Periodic screening of other lead exposed workers is indicated to detect early lead-related renal disease. This could best be accomplished by measuring creatinine clearance and urinary concentrating ability every six months on lead exposed workers. This is especially important for workers with many years of lead exposure. Since these indicators become abnormal rather late in the course of renal disease, more sensitive methods should be sought to detect lead nephropathy in its early, reversible stage.

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TABLE 1. Routine Renal Function Tests, Eagle Picher Industries, July 1976

Subject	BUN Level (mg/100ml)	Creatinine Level (mg/100ml)	Routine Urinalysis
1	18	1.1	Normal
2	15	0.9	normal
3	25	1.2	hyaline casts, 5-6 wbc/hpf
4	26	1.2	granular casts
5	17	0.9	normal
6	24	0.8	normal
7	15	0.8	normal
8	18	0.9	normal
9	18	1.0	normal
10	19	1.0	normal
11	15	1.0	normal
12	18	1.0	normal
13	15	1.0	normal
14	18	1.2	normal
15	15	1.0	normal
16	13	0.7	normal
17	27	1.9	normal
18	23	1.4	normal
19	16	0.8	normal
Normal range	≤ 22	≤ 1.5	

TABLE 2. Results of Renal Function Test' Missouri 1976

SUBJECT	AGE	DURATION OF LEAD EXPOSURE (YEARS)	BLOOD LEAD LEVEL (µg/100ml)	CREATININE CLEARANCE (ml/min/1.73 sq.m BSA)	FASTING URINE OSMOLALITY (mosm/liter)	LEAD CLEARANCE RATE* (ml/min)
1	56	7	154	85		.07
2	48	20	66	142		.82
3	37	20	35	82	871	1.46
4	47	23	71	72	588	0.10**
5	45	8	87	128	1020	0.61
6	53	23	61	91	1025	0.97
7	52	26	61	115	650	0.70
8	38	20	123	109	608	0.94
9	60	25	75	75	278	0.30
10	42	21	66	96	1180	0.36
11	47	7	48	108	820	1.09
12	53	29	96	89	708	0.10
13	35	13	56	109	965	1.13
14	62	16	105	97	912	1.01
15	52	25	78	73	286	0.25
16	53	20	92	108	912	0.04**
17	51	7	80	65	704	2.04
18	52	31	55	43	652	0.80
19	29	4.5	58	112	1114	0.92
Normal Range			< 60	>91	800-1300	

*See text for calculation formula

**Urine lead level for these 2 subjects below analytical detection limit (0.01µg/liter); urine concentration estimated to be .005µg/liter (½ detection limit) for these 2 samples.

TABLE 3. Hematologic Testing, Eagle Picher Industries, July 1976

Subject	Hemoglobin Level (gm/100ml)	Hematocrit (vol. %)	Erythrocyte Protoporphyrin (µg/100ml rbc)	Urinary Delta ALA (mg/100ml)
1	15.5	44.1	502	1.46
2	15.2	44.9	361	0.35
3	14.8	42.7	260	0.51
4	12.6	36.7	468	0.18
5	15.1	44.2	464	0.89
6	14.8	43.1	142	1.82
7	14.2	41.8	449	0.69
8	12.3	36.1	426	0.85
9	14.7	43.5	548	0.37
10	15.4	45.0	351	0.33
11	13.8	39.9	174	1.14
12	15.3	44.3	237	0.62
13	15.0	43.1	164	1.60
14	13.0	43.1	164	1.60
15	14.0	41.1	200	0.92
16	14.8	42.2	278	1.92
17	13.2	40.1	401	1.27
18	14.9	44.1	532	0.78
19	14.3	42.5	244	0.91

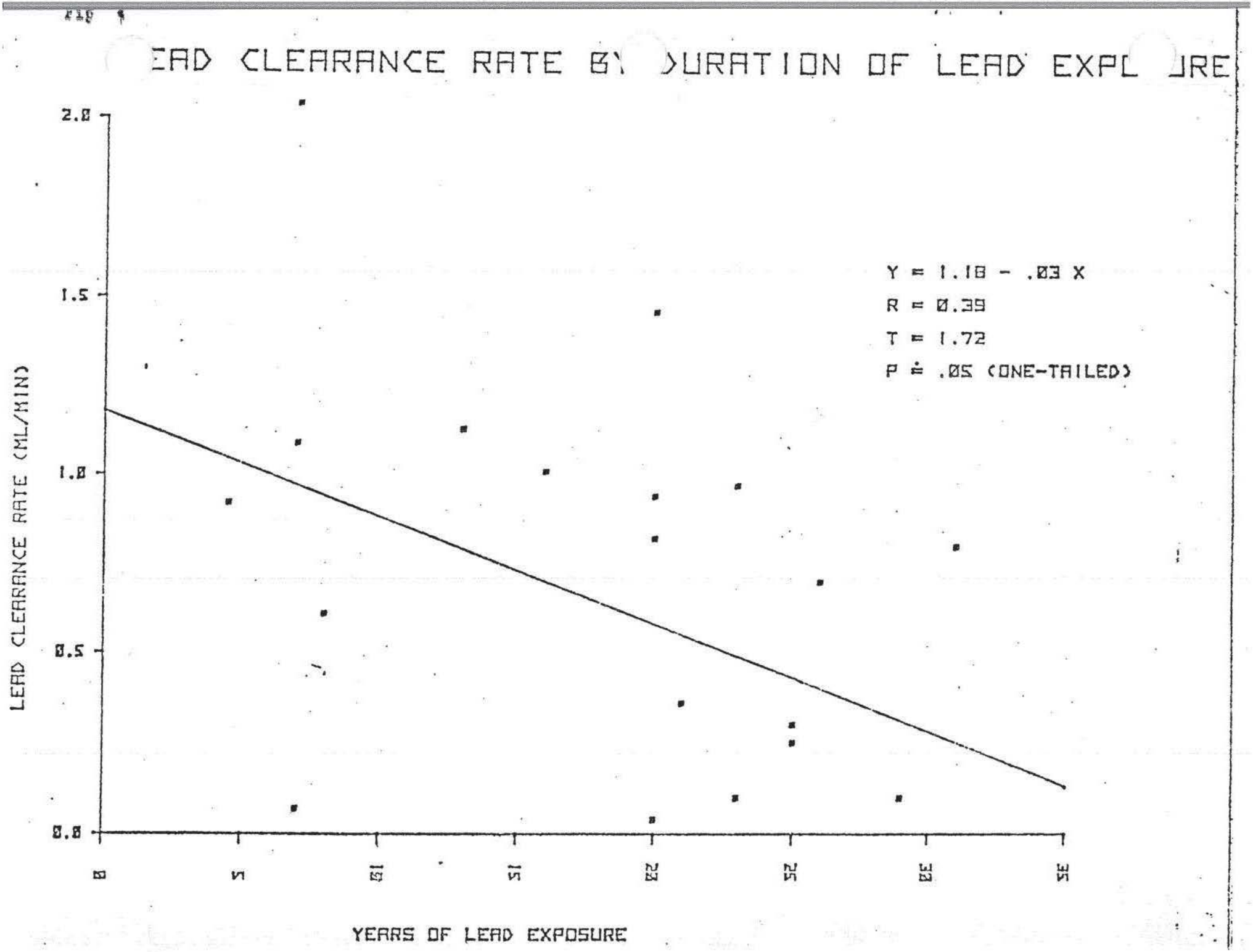
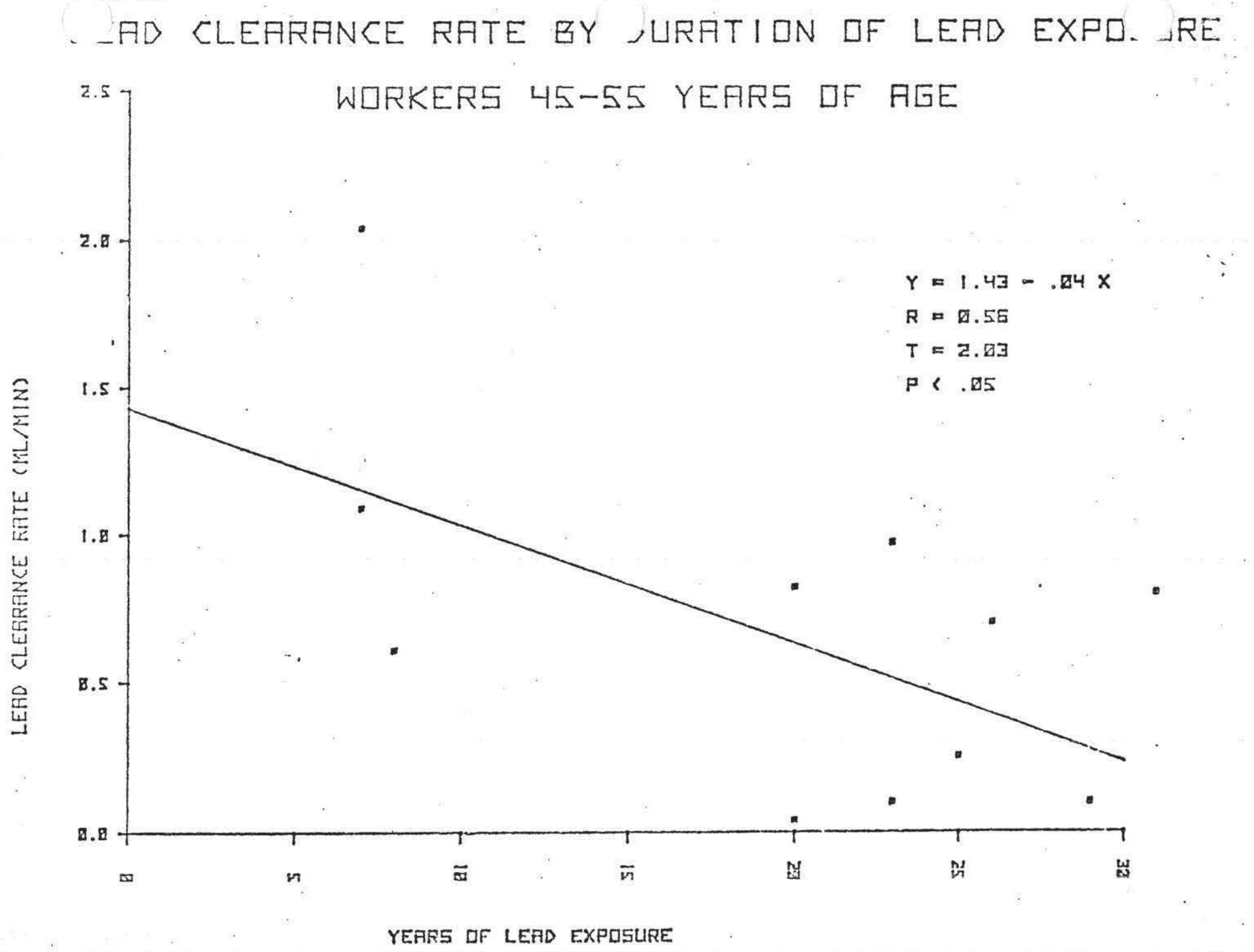

EAD CLEARANCE RATE BY DURATION OF LEAD EXPL JRE
Y = 1.18 - .03 X
R = 0.39
T = 1.72
P = .05 (ONE-TAILED)
LEAD CLEARANCE RATE (ML/MIN)
2.0
1.5
1.0
0.5
0.0
0
5
10
15
20
25
30
35
YEARS OF LEAD EXPOSURE

Fig. 2


LEAD CLEARANCE RATE BY DURATION OF LEAD EXPOSURE
WORKERS 45-55 YEARS OF AGE
Y = 1.43 - .04 X
R = 0.56
T = 2.03
P < .05
LEAD CLEARANCE RATE (ML/MIN)
2.5
2.0
1.5
1.0
0.5
0.0
0
5
10
15
20
25
30
YEARS OF LEAD EXPOSURE