

Health hazards among copper smelter workers

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ENVIRONMENTAL SCIENCES LABORATORY
MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK

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CHAPTER I

Populations, material and methods

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Introduction

Lead, cadmium and arsenic emissions from a large copper smelter were found to result in environmental contamination and significant absorption in segments of the population living in the immediate vicinity.

An increase in blood (Pb-B) and hair (Pb-H) lead levels, and a corresponding inhibition of amino-levulinic acid dehydratase (ALA-D) were found to be more prominent in school children; higher levels of cadmium and arsenic in hair were also present. Soil contamination through fall-out from smelter emissions was found to be the major source; the higher Pb, Cd and As levels in school children were thought to be the result of childhood activities.¹ Blood lead levels generally were not found to exceed 40 µg/dl. However, a significant proportion, (especially among children) had Pb-B levels higher than 30 µg/dl, the upper limit of acceptable Pb-B levels in children.

A mortality study comparing the population of the town in which the copper smelter operates with that of the province of Québec and with that of two comparable communities, has detected an excess of lung cancer in the smelter town population. Arsenic exposure from smelter emissions is suspected to be the etiologic agent for the excess lung cancer mortality. The copper smelter, operating since 1927, is known to generate monthly emissions of 110 tons of lead, 25 tons of arsenic, 13 tons of cadmium, as well as large amounts of sulfur dioxide.²

With the information on environmental contamination documenting undue exposure to the population living around the smelter, the need for a comprehensive assessment of the health status of the smelter employees was recognized.

Study population

The study population consisted of all employees of the copper smelter listed on the October 4, 1979 seniority list who had six or more months employment with the Noranda Company, and all individuals listed on the rolls of the Quarter Century Club (membership in which required 25 years

employment with the company), who had retired or ceased employment with the Noranda Company and were living in the Rouyn-Noranda area of Québec. Invitations were issued irrespective of the current health status of the individuals. Among those on the seniority list were 23 individuals who were temporarily on leave of absence because of physical incapacity, generally from trauma. Of the 819 current employees invited, 739 (90.2%) attended the examinations. Of the 185 individuals who had terminated employment with Noranda and who were invited, 92 (49.7%) attended the examinations. This group constituted the invited study population of 831 individuals. Additionally, during the course of the examination, 102 individuals not listed on the October seniority list or in the Noranda Quarter Century Club booklet participated in the examinations. Most were individuals who had been employed at Noranda but for periods less than 25 years.

The workforce under study were employed in two principal activities, the mining of gold and copper ores in the western portion of Quebec and in tasks associated with the smelting of these ores (and other copper ores) in the Noranda smelter. The majority of the men currently employed had only smelter employment. However, a significant number of those currently employed had previous mining experience, either at Noranda or at another of the many mining operations in the area. When the principal Noranda mine ceased operations in 1976, those employed by the company were offered work in the smelter. These tended to be individuals with relatively long-term employment. The group which had terminated employment with Noranda consisted of individuals who were largely miners in earlier years, although some smelter workers had achieved retirement status. Thus, the examinees consisted of a group, largely younger workers, whose principal employment was in the Noranda smelter, a second group, largely older workers, whose principal employment was only in hard rock mining and, as described previously, a third group that included individuals with both mining and smelting experience, the mining experience preceding that of the smelter. Because of the distinctly different exposures in these work activities, the work experience of these groups will be analyzed separately. The age distribution of each of the three groups is shown in Table 1-1. Tables 1-2 and 1-3 list the distribution of years from onset of employment and years

Table 1 - 1

Age distribution of examined (invited and uninvited)
smelter and mine workers

<u>Age</u>	<u>Invited and examined</u> E M P L O Y M E N T			<u>Uninvited but</u> <u>examined</u>
	<u>Miners</u>	<u>Smelter</u> <u>workers</u>	<u>Mine and</u> <u>smelter work</u>	
20 - 29	5.4 (4)	23.4 (97)	6.5 (22)	3.0 (3)
30 - 39	7.7 (6)	29.4 (122)	15.4 (52)	8.9 (9)
40 - 49	7.7 (6)	16.4 (68)	15.7 (53)	10.9 (11)
50 - 59	29.5 (23)	17.4 (72)	39.6 (134)	43.6 (44)
60 - 69	34.6 (27)	10.4 (43)	20.4 (69)	24.8 (25)
70 +	15.4 (12)	3.1 (13)	2.4 (8)	8.9 (18)
Total	78	415	388	101
Active	35	382	299	-
Retired or terminated	39	26	27	101*
Incapacitated	4	7	12	-

* A small number were employed with companies other than Noranda.

Table 1 - 2

Distribution of years from onset of employment and years of employment for individuals employed in smelter work

Years of employment	<u>Years since onset of employment</u>					Total
	0 - 9	10 - 19	20 - 29	30 - 39	40+	
0 - 9	138	8	0	1	0	147
10 - 19	0	122	8	3	0	133
20 - 29	0	0	85	6	1	92
30 - 39	0	0	0	33	4	37
40 +	0	0	0	0	6	6
Total	138	130	93	43	11	415

Table 1 - 3

Distribution of years from onset of employment and
years of employment for individuals employed in mining

Years of employment	<u>Years since onset of employment</u>					Total
	0 - 9	10 - 19	20 - 29	30 - 39	40+	
0 - 9	4	0	0	0	0	4
10 - 19	0	5	3	1	0	9
20 - 29	0	0	10	16	3	29
30 - 39	0	0	0	18	14	32
40+	0	0	0	0	4	4
Total	4	5	13	35	21	78

of employment for individuals employed in smelter work and in mining work. As can be seen, the distribution of years from onset of employment and years of employment were virtually identical for those employed in smelter work, reflecting the currently employed status of such individuals. On the other hand, many miners have retired and their years from onset of employment generally were greater than the years of employment. Table 1-4 lists the distribution of employment for those individuals who were employed in both mining and smelter work. Two distinct groups are seen, one with short-term mining experience who entered smelter work at a relatively young age and one with long-term mining work, mostly in the Noranda mine, who entered work in the smelter during the 1970s.

Thirty-eight separate job categories were used for the classification of work activities within the smelter. These are listed in Appendix 1 along with a description of the work. Because of the limited number of individuals employed in many of these job categories, broader work categories were established for the comparative analysis of health effects. These are listed in Appendix 2.

Groups (active workers, retirees and miners) as described throughout the text were created after case-by-case review of a preliminary classification. This classification included: actively working, disabled, non-cohort but worked at Noranda for less than 25 years, non-cohort and never worked at Noranda, retired and unknowns. Twelve individuals were not included because they had never worked at a Noranda mine or smelter. There were 931 males and one female. Statistical analysis was performed on data for males only.

Job categories (listed in Chapter II) refer to the currently held jobs.

Quality control and computer-based procedures

All questionnaires were designed for computer analysis. When all data sets were completed, over 700 pieces of information were available for each of the 932 individuals.

Table 1 - 4

Distribution of years of employment for individuals
employed in both mining and smelter work

Years of mine work	Years of smelter work				Total
	0 - 9	10 - 19	20 - 29	30+	
0 - 9	64	41	40	16	161
10 - 19	22	17	6	2	47
20 - 29	93	8	0	0	101
30+	28	1	0	0	29
Total	207	67	46	18	338

Because of the magnitude of the data, careful consideration was given to quality control, particularly proofreading. There were two types of proofreading: literal and semantic.

There were several stages where a literal proofreading was performed:

- Before the subject left the site to determine whether all the forms and all the data-entry boxes had been completed;
- Before dismembering the booklets containing the forms which later on were sent for professional keypunching;
- During keypunching (two independent tapes were punched and checked against each other for inconsistencies); and
- After the tapes were returned.

In addition, a semantic proofreading was performed particularly on medical and laboratory data. Examples of semantic proofreading were:

- Inconsistency (or unlikelihood) of year of reported symptom, condition, job held, age, etc.;
- Outlying values of laboratory data (unusually low or high values) which were detected by sorting by increasing order of magnitude and later verified against individual records.

Five computer languages and/or statistical packages were used to create data sets and/or perform statistical analysis. WYLBUR (an editing language) was used to create the first version of the 25 original data sets. SAS was used to create the permanent data bank, update versions of tape backups, proofreading and most of statistical analysis, SPSS was used for scattergrams and BMDP for specific tests (such as Mallows' Cp) not available in other statistical packages. Finally, APL was used to create the individual medical reports.

The examination

All examinations were carried out using forms appropriate for computer analysis. These included:

- Personal data necessary to send individual medical reports (to be explained below);
- Detailed occupational history before the smelter (and/or mines) and at the smelter (and/or mines);
- Protective equipment and personal hygiene;
- Respiratory questionnaire (MRC);
- Smoking history;
- Medical history, including past use of medications;
- Alcohol intake;
- Special questionnaire with review of symptoms (particularly those suspected in metal toxicity); and
- Physical examination.

Laboratory procedures

Laboratory tests included:

- Zinc protoporphyrin (ZPP) determination in whole blood with a portable hematofluorometer^{3 4};
- Blood and urinary cadmium (Cd-B and Cd-U), respectively. Urinary cadmium values were corrected for urine density and for creatinine levels;
- Urinary arsenic (As-U);
- Urinary β -2 microglobulins;
- Complete blood count;
- Blood biochemistry analysis for creatinine, blood urea nitrogen (BUN), potassium, glucose, albumin, total protein, calcium, phosphorus, SGOT, SGPT, and alkaline phosphatase;
- Pulmonary function tests (described in Chapter VII);
- Chest X-ray films (described in Chapter VIII);
- A short battery of neurobehavioral performance tests designed for the detection of early signs of lead toxicity (described in Chapter IV);
- Oculographic tests for early signs of metal toxicity (described in Chapter V); and
- Nerve conduction velocity determinations for detection of lead and/or arsenic toxicity affecting the peripheral nervous system (described in Chapter VI).

Individual reports were accompanied by a letter with the highlights of the medical and laboratory findings. Letters were written in English or French according to the workers' wishes.

Finally, each of the 932 individual reports and letters was reviewed by Dr. Ruth Lilis, Associate Director for Clinical Studies and Dr. Irving J. Selikoff, Director of the Environmental Sciences Laboratory, Mount Sinai School of Medicine.

Statistical analysis of data

This report is a review of findings and includes analysis of very extensive data, (close to 750,000 items of information). Numerous tables and figures are used as abstracts of large amounts of data.

To maintain coherence throughout the report, we adhered to the following rules:

- Categorical data across the groups (Yes-No type) were analyzed by chi-square tests;
- Ordinal data by means of non-parametric tests; and
- Continuous data by means of parametric tests.

Each continuous variable was tested for normality and transformations were used if and when such transformations improved the normality of the distribution. The criterion for normality was the probability value associated with D in the Kolmogorov-Smirnov test.

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Appendix 1

Noranda Smelter Operations1. Open Pit (321)*

An open pit mine operated near the smelter provides ore used as flux in the reactor and furnace. A primary crusher at the pit reduces the size of the ore to less than 10 inches in diameter.

2. Crusher (321)

A secondary crusher operating near the smelter reduces ore from 10 inches to as small as one-half inch in diameter. The operation of this facility has been significantly reduced in recent years as much of the ore now used arrives as concentrate.

3. Concentrator (211)

Ore is brought from the crusher ball mill in a wet state where beneficiation by floatation occurs. Also in this facility are located the

- a) concentrate unloading shed where material arriving by rail is discharged (211), and the
- b) batching plant where concentrate is mixed with flux prior to being sent to the reactor (321).

Previously, a cyanamide gold recovery plant operated in the concentrator facility.

4. Roaster (333)

Prior to modernization, a roaster was utilized as the primary step in the smelting process. Here concentrates were heated with air and silica flux to form a slag of iron dioxides and other unwanted materials. Previously, a copper sulfide matte was then sent to the smelting furnace, the next step in the process. Currently the roaster serves primarily for mixing purposes with the smelting being done in the furnace and the reactor.

5. Furnace (333)

The reverberatory furnace is one of the two principal smelting devices to separate the unwanted wastes from the copper sulfide matte. The feed consists of unroasted concentrates and flux materials, limestone and silica. At the furnace a Cottrell dust collector collects particulate emission from this furnace. A crew of men is assigned for cleaning purposes and for directing the collected dust back to the roaster or furnace.

6. Reactor (333)

The newest smelting device at Noranda is the reactor which utilizes a continuous feed process. The reactor is fed with coal, concentrated flux and crude oil. The output is a relatively high purity copper which may not need a subsequent converting process.

7. Converter (223 feeding)

The converter takes the copper matte produced in smelting and converts it to a crude form of refined copper which is approximately 99% pure. The matte is transported on a track in large containers and fed to the converter. Oxygen flux and scrap metal are added to the mix as appropriate.

8. Casting (122)

The output of the converter is cast into anodes which are then sent for electrolytic refining elsewhere.

9. Inside Shops

- a. Plate shop: steel cutting and welding of all machinery parts are completed here. (111)
- b. Machine shop: tool makers; all heavy mechanical work and repair of machinery. (222)
- c. Electrical shop: (111)

10. Scrap Building (222)

Unloading, cutting and melting of scrap material. Two furnaces are nearby.

11. Power House (000)

Located behind the furnace, functions to meet power needs of equipment.

12. Boilers (313)

A team of workers is engaged in cleaning the boilers.

13. Oxygen Plant (000)

Maintenance of pipes and oxygen regulation.

14. Slag Department (222)

An outside shop in which the slag is cooled with water, producing steam as a byproduct, and recycled.

15. Sample Mill (321)

Gathering of samples from all over the plant and crushing them into dust.

16. Railroad Construction Yard (000)

Outside construction.

17. Saw Mill; Lumber Yard; Oil Storage (111)

Painters and carpenters who work all over the plant. Also workers from oil storage change filters all over the plant.

18. Smelter Maintenance

- a. Painters (222)
- b. Carpenters (222)
- c. Riggers (333)
- d. Heavy Equipment Maintenance (111)
- e. Bricklayers (333)
- f. Pipefitters/plumbers (322)
- g. Welders (222)
- h. Laborers, inside (333)
- i. Clean yard work (000)
- j. Office (000)
- k. Warehouse (000)

* The numbers in parenthesis indicate the estimated exposure to dusts, metals and SO₂, respectively, on a four point scale from 0 (low) to 3 (high).

Appendix 2

Exposure groupings and relative exposures to dust, metals and SO₂

Broad exposure category	Work areas (refer to Appendix 1)	Exposures
Pit, crusher, concentrator	1, 2, 3	High dust; low SO ₂
Roaster, reactor, furnace	4, 5, 6	High dust, metals, SO ₂
Converter	7	Moderate dust, metals; high SO ₂
Anode casting	8	Low dust; moderate metals, SO ₂
Inside shops	9	Relatively low dust, metals, SO ₂
Maintenance	18	Moderate dust, metals, SO ₂
Other smelter	rest	Mixed exposures

Chapter II

Distribution of blood lead, blood cadmium, urinary cadmium
and urinary arsenic levels in employees of a copper smelter

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Introduction

A cross-sectional medical examination of a copper smelter work force included measurement of blood lead (Pb-B), blood zinc protoporphyrin (ZPP), blood cadmium (Cd-B), urinary cadmium (Cd-U) and urinary arsenic (As-U); it was known that lead, cadmium and arsenic impurities were present in the copper concentrate and that there was potential for exposure to these metals.

For further details on the background of this study, see Chapter I.

Population and Methods

A cross-sectional medical examination of workers employed at a copper smelter was conducted; this included measurements of blood lead (Pb-B), blood zinc protoporphyrin (ZPP), blood cadmium (Cd-B), urinary cadmium (Cd-U) and arsenic (As-U). Lead and cadmium in blood was determined by graphite furnace atomic absorption spectrophotometry, using a Perkin-Elmer atomic absorption spectrophotometer, Model 5000, with a 500 model graphite furnace.^{1 2} The detection limit for blood lead was 10 µg/l and the reproducibility 10%. The laboratory, Centre de Toxicologie du Québec, participates in the Centers for Disease Control Analytical Proficiency Program for blood lead. In 1980, the results of the laboratory were within range for all 36 samples sent by the CDC. In 1981, 35 out of 36 of the results were within range. The detection limit for blood cadmium was 0.2 µg/l with a precision of ± 5%.

Graphite furnace atomic absorption spectrophotometry was also used for determination of cadmium and total arsenic in urine; the detection limit was 0.2 µg/l for urinary cadmium, and the precision was ± 5%. For urinary arsenic, the detection limit was 10 µg/l and the precision of the test 10%. A calibration curve was prepared by adding As to a pool of urine to yield concentrations between +0 and 200 µg/l.

Zinc protoporphyrin in blood was determined on capillary blood samples obtained by finger puncture utilizing a hematofluorometer (Aviv Biomedical).^{3 4 5}

Life-long occupational history and past medical history were recorded. Physical examination, clinical biochemistry, measurement of urinary β_2 -microglobulin excretion, chest X-ray film, and pulmonary function tests were also performed. Evaluation of the nervous system included neurobehavioral performance tests, nerve conduction velocity measurements and oculomotor function studies. We report here on the distribution patterns of indicators of lead, cadmium and arsenic absorption.

The examined population comprised 680 active smelter employees, 96 retired smelter employees (or ex-smelter employees) and 144 men who had never been employed in the smelter itself, but had worked as miners in copper and gold mines in the area (the company had, until recently, operated its own copper mine).

Age distribution of the 920 workers examined is presented in Table 2-1. The active employees comprised only 8.2% of persons over 60 years of age, while most of the retirees (85.4%) and miners (80%) were over 50 years of age. Duration of copper smelter employment and years from onset of smelter employment are presented in Table 2-2. More than half of the active employees had been employed for over 10 years.

Using information from industrial hygiene studies of copper smelters,⁶ the large variety of job designations in the smelter were classified, with regard to potential exposure to Pb, Cd and As into four categories: minimal, low, medium and high (Table 2-3). The mobility of employees through several job categories was recognized, especially for those with long-term employment; an "equalization" effect was therefore possible. For certain parameters, when recent exposure was thought to be of special relevance, analysis according to current job assignment was undertaken.

Table 2 - 1

Age distribution of copper smelter workers

Years	Smelter workers				Miners	
	Active		Retired		N	%
	N	%	N	%		
< 30	143	21.0	3	3.1	5	3.5
31 - 40	161	23.7	6	6.2	8	5.6
41 - 50	132	19.4	5	5.2	16	11.1
51 - 60	188	27.6	23	24.0	53	36.8
> 60	56	8.2	59	61.4	62	43.1

Table 2 - 2

Duration of copper smelter employment

<u>Years</u>	<u>Active workers</u>		<u>Retirees</u>	
	N=680		N=96	
	N	%	N	%
< 5	178	26.2	20	20.8
5 - 9.9	151	22.2	10	10.4
10 - 19.9	197	29.0	20	20.8
20 - 29.9	119	17.5	21	21.9
<u>≥ 30.0</u>	35	5.1	25	26.0

Duration from onset of copper smelter employment

<u>Years</u>	<u>Active workers</u>		<u>Retirees</u>	
	N=680		N=96	
	N	%	N	%
< 5	167	18.7	11	11.5
5 - 9.9	151	22.2	5	5.2
10 - 19.9	209	30.7	15	15.6
20 - 29.9	132	19.4	19	19.8
<u>≥ 30.0</u>	61	9.0	46	47.9

Table 2 - 3

Classification of active copper smelter employees
according to intensity of Pb, Cd, As exposure

Exposure category		Minimal	Low	Medium	High	Total
All active smelter employees	N	81	192	188	218	
	%	11.9%	28.3%	27.7%	32.1%	
Present smokers	N	49	102	103	128	382
	%	12.8%	26.7%	27.0%	33.5%	56.3%
Ex-smokers	N	21	55	52	47	175
	%	12.0%	31.4%	27.7%	21.6%	25.8%
Nonsmokers	N	11	35	33	43	122
	%	13.6%	18.2%	17.5%	19.7%	18.0%

Results

Lead

The distribution pattern, median and mean Pb-B levels are presented in Table 2-4. The active smelter employees had significantly higher Pb-B levels than retirees and miners. Only a very small proportion (less than 1%) had Pb-B levels of 60 $\mu\text{g}/\text{dl}$ or higher, indicating that recent lead absorption did not represent a major hazard at the time of the examination. In fact, 83% of the active smelter workers had Pb-B levels below 40 $\mu\text{g}/\text{dl}$. Zinc protoporphyrin distribution patterns, median and mean values are presented in Table 2-5. Similar to what was found for blood lead, significantly higher levels were detected in active smelter employees; the proportion of those with ZPP levels of 100 $\mu\text{g}/\text{dl}$ and above was 16.7%. The relationship between Pb-B and ZPP levels was similar to the one (Figure 2-1) found for other populations with long-term stable lead exposure.^{7 8}

Cadmium

Distribution patterns, median and mean values of Cd-B are presented in Table 2-6. Findings were similar to those described for Pb-B and ZPP: Cd-B was significantly higher in active smelter employees. In non-occupationally exposed adults, the median value of Cd-B has been reported to be approximately 1.5 $\mu\text{g}/\text{l}$.⁹ In a study of a population living in a town in Belgium, environmentally contaminated with cadmium,¹⁰ the mean Cd-B was found to be 1.6 $\mu\text{g}/\text{l}$ (range 0.5 - 5.5 $\mu\text{g}/\text{l}$) as compared to a mean value of 1.2 $\mu\text{g}/\text{l}$ (range 0.2 - 4.5 $\mu\text{g}/\text{l}$) in another, non-contaminated area. Although Cd-B levels were significantly higher in active smelter employees, as compared to those found in the general population studies mentioned, somewhat elevated levels were also found in retirees and miners; this probably reflects environmental cadmium contamination in the vicinity of the smelter. However, a residual effect of past occupational exposure in retired smelter employees and miners is also a possible explanation.

Distribution patterns, median and mean values of urinary cadmium are presented in Table 2-7. Mean and median Cd-U were highest in retired smelter

Table 2 - 4

Distribution, median and mean values of blood lead levels (PbB)

<u>PbB $\mu\text{g}/\text{dl}$</u>	Active smelter workers N=680		Retirees N=96		Miners N=144	
	N	%	N	%	N	%
< 40	566	83.2	94	97.9	141	97.9
40 - 59	111	16.3	2	2.1	3	2.1
60 - 79	3	0.4	0	-	0	-
Median	30.4		19.5		17.4	
Mean \pm SD	31.1 \pm 9.69		20.2 \pm 6.62		19.2 \pm 7.07	
t			[$\rightarrow\rightarrow\rightarrow\rightarrow$ 14.1 $\leftarrow\leftarrow\leftarrow\leftarrow$] p<0.0001		[$\rightarrow\rightarrow\rightarrow\rightarrow$ 1.15 $\leftarrow\leftarrow\leftarrow\leftarrow$] n.s.	
			[$\rightarrow\rightarrow\rightarrow\rightarrow\rightarrow\rightarrow\rightarrow\rightarrow\rightarrow\rightarrow$ 17.1 $\leftarrow\leftarrow\leftarrow\leftarrow\leftarrow\leftarrow\leftarrow\leftarrow\leftarrow\leftarrow\leftarrow$] p<0.00001			

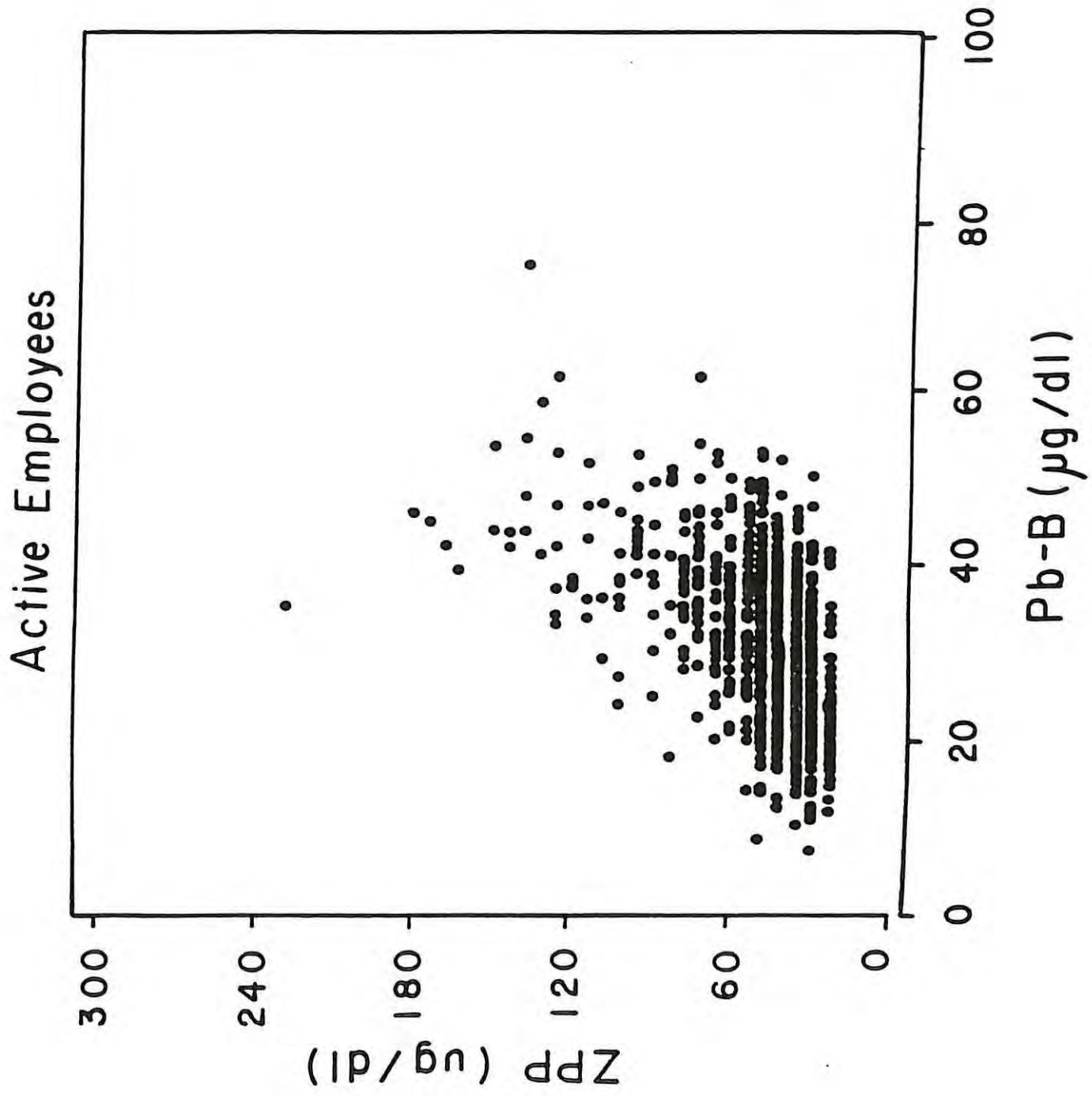


Figure 2 - 1

employees; the difference between active and retired smelter employees was statistically significant. Cd-U did not exceed 10 $\mu\text{g/g}$ creatinine in any of the workers; this level is considered to be the critical level for renal impairment. Nevertheless, in 12.6% of active and 25% of retired smelter employees, Cd-U was 2 $\mu\text{g/g}$ creatinine or higher; such levels are very uncommon in the absence of significant exposure.^{11 12 13} A strong positive correlation was found between Cd-B and Cd-U in active smelter employees (Figure 2-2 and Figure 2-3). In retired smelter employees, an even stronger correlation was found (Figure 2-4). This is most probably due to the effect of variation in absorption among active employees, partly related to their different job assignments with different levels of exposure, and varying duration of exposures.

Significant correlations between Pb-B and Cd-B (Figure 2-5), Pb-B and Cd-U (Figure 2-6) suggest that exposures to lead and cadmium have a common source in the impurities of copper concentrates used in the smelter.

Distribution patterns, median and mean values for urinary arsenic are presented in Table 2-8 ($\mu\text{g/l}$, density corrected) and Table 2-9 ($\mu\text{g/g}$ creatinine); significantly higher levels were found among the active smelter employees. As-U levels were also significantly correlated with Pb-B levels (Figure 2-7).

The effect of smoking, known to be an important factor in cadmium absorption and body burden, was also investigated. Cd-B was found to be significantly higher in smokers in all subgroups (active employees, retirees and miners). Among present smokers, active employees had significantly higher Cd-B than miners; active smelter employees who had never smoked, also had significantly higher Cd-B than miners who had never smoked (Table 2-10). With regard to Cd-U, the highest levels were found in retirees, and more specifically in smoking retirees. For non-smokers, the active smelter employees had significantly higher Cd-U than the retirees (Table 2-11).

By comparison, the effect of smoking habits on Pb-B and As-U levels was found to be negligible (Table 2-12; Figure 2-8).

Table 2 - 9

Urinary arsenic ($\mu\text{g/g}$ creatinine) in
copper smelter employees

AsU $\mu\text{g/g}$ creatinine	Active employees		Retirees		Miners	
	N	%	N	%	N	%
< 20	440	64.7	78	81.2	120	83.3
20 - 49.9	197	29.0	15	15.6	21	14.6
50 - 99.9	37	5.4	2	2.1	1	0.7
\geq 100	6	0.9	1	1.0	1	1.4
Median	17.0		10.0		10.0	
Mean \pm SD	21.7 \pm 21.1		16.2 \pm 18.1		14.2 \pm 17.0	
t	[→→→2.31←←←]		[→→→0.81←←←]		[→→→0.81←←←]	
	p=0.02		n.s.		n.s.	
	[→→→→→→→→→4.35←←←←←←←←←←←←←←←←←]					
	p=0.0001					

invol As = 74.91 μg

Table 2 - 10Blood cadmium $\mu\text{g}/\text{l}$ (mean \pm SD)

	<u>Smokers</u>	<u>Never Smoked</u>	<u>t</u>	<u>p</u>
Active copper smelter employees	6.93 \pm 4.10	1.04 \pm 0.96	25.9	< 0.0001
Miners	5.56 \pm 3.64	0.57 \pm 0.38	11.5	< 0.0001
t	2.66	3.97		
p	0.008	0.0002		

Table 2 - 11

Urinary cadmium ($\mu\text{g/g}$ creatinine)
and smoking habits

	Smokers		Never smoked		
	Cd U $\mu\text{g/g}$ creatinine				
	Mean	SD	Mean	SD	
Active smelter employees	1.43 \pm 1.17		0.58 \pm 0.48		
	[t=4.12	[t=10.8	[t=3.02	[
	[p<0.0001	[p<0.0001	[p=0.006	[
Retirees	2.26 \pm 1.27		0.34 \pm 0.23		n.s.
	[t=2.34	[t=8.87	[t=1.01	[
	[p=0.02	[p<0.0001	[n.s.	[
Miners	1.69 \pm 1.13		0.48 \pm 0.45		
		[t=6.85			
		[p<0.0001			

Table 2 - 12Blood lead levels and smoking habits

	<u>Smokers</u>		<u>Nonsmokers</u>		<u>t</u>
	<u>N</u>	<u>PbB $\mu\text{g/dl}$ mean\pmSD</u>	<u>N</u>	<u>PbB $\mu\text{g/dl}$ mean\pmSD</u>	
Active smelter employees	381	31.7 \pm 9.5	121	30.7 \pm 9.8	0.98 n.s.
Miners	73	20.5 \pm 8.0	21	18.7 \pm 8.4	0.86 n.s.
	t	9.44		5.27	
	P	0.0001		0.0001	

Active Employees

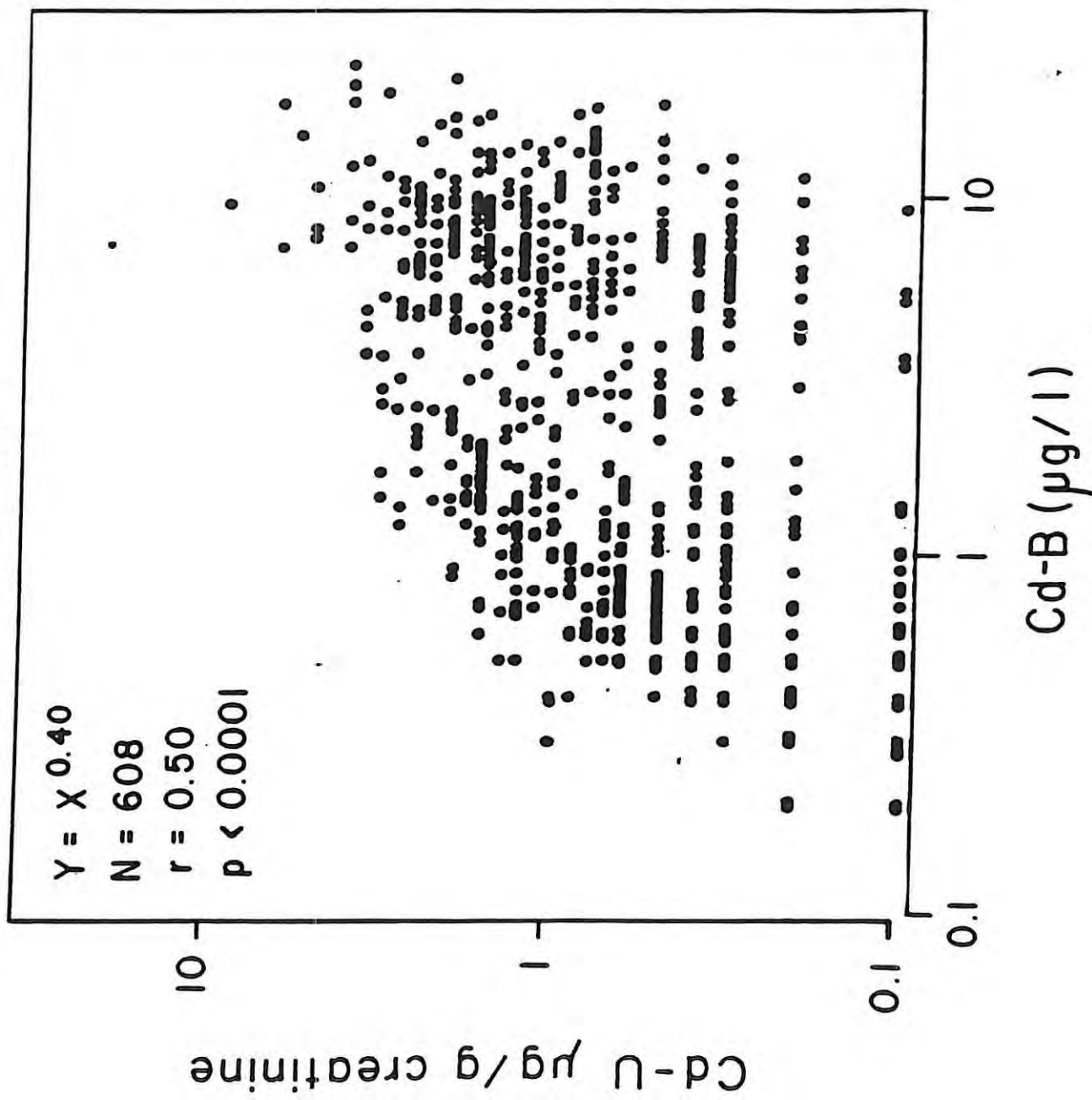


Figure 2 - 2

Active Employees

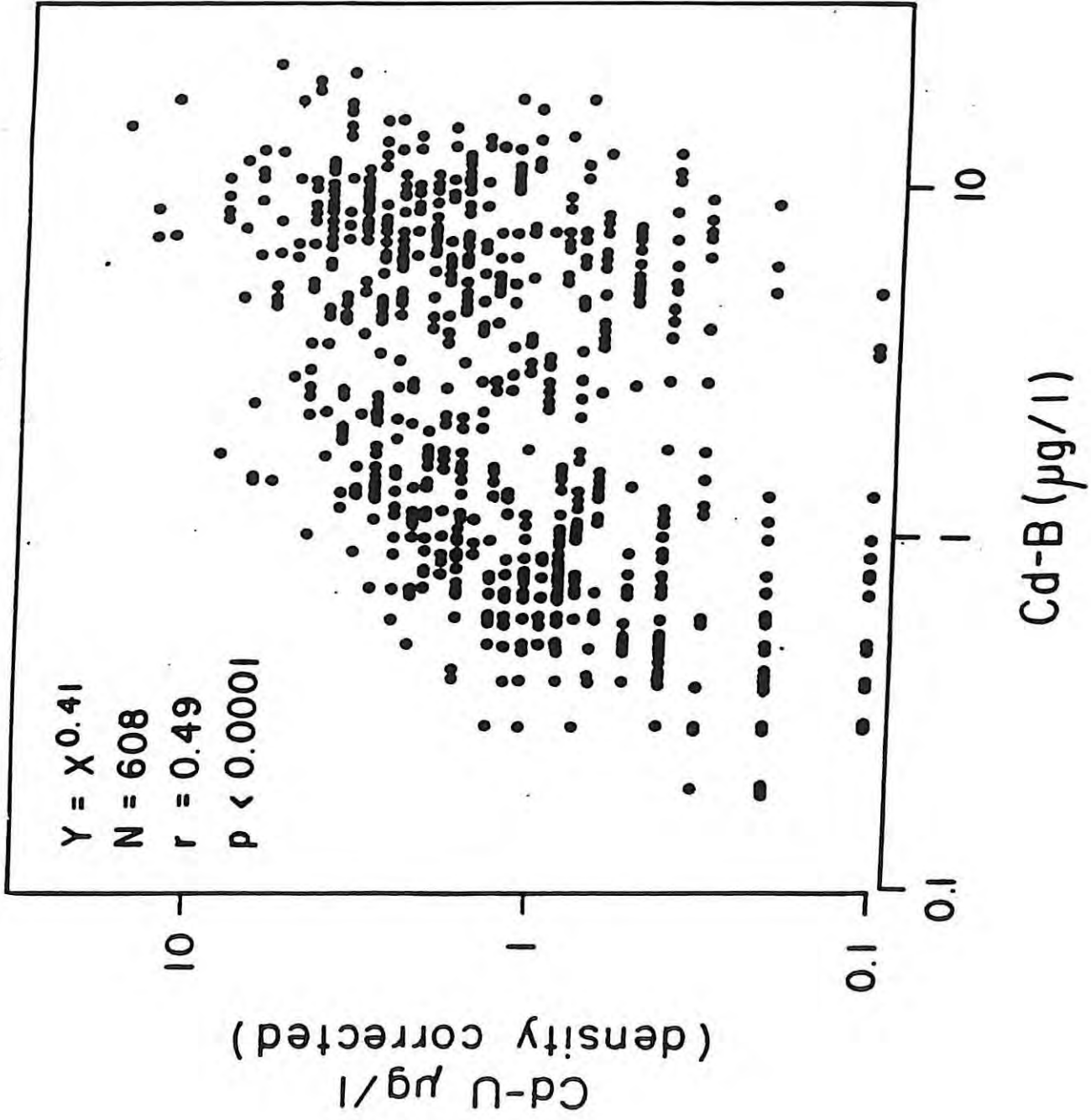


Figure 2 - 3

Retirees

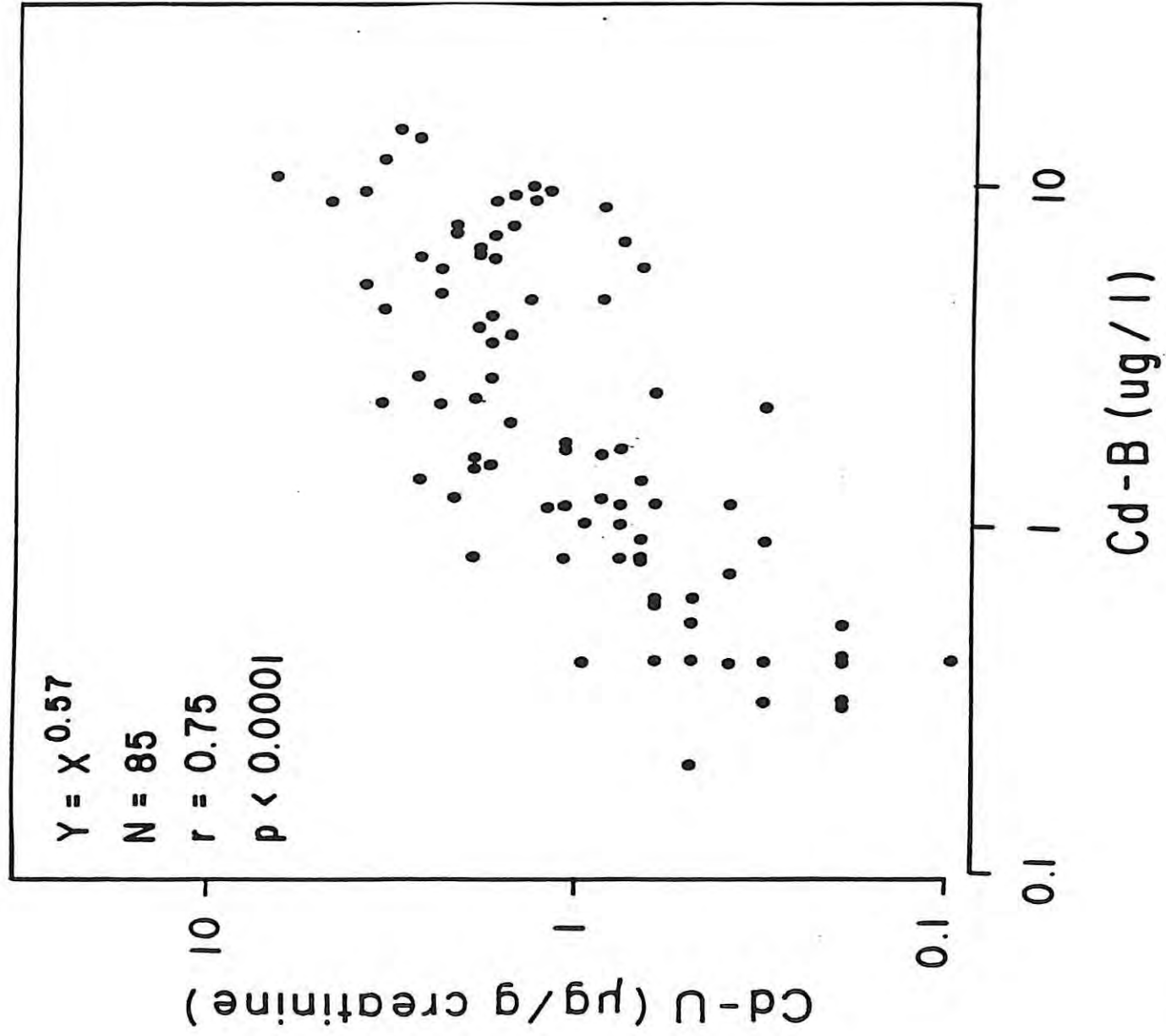


Figure 2 - 4

Active Employees

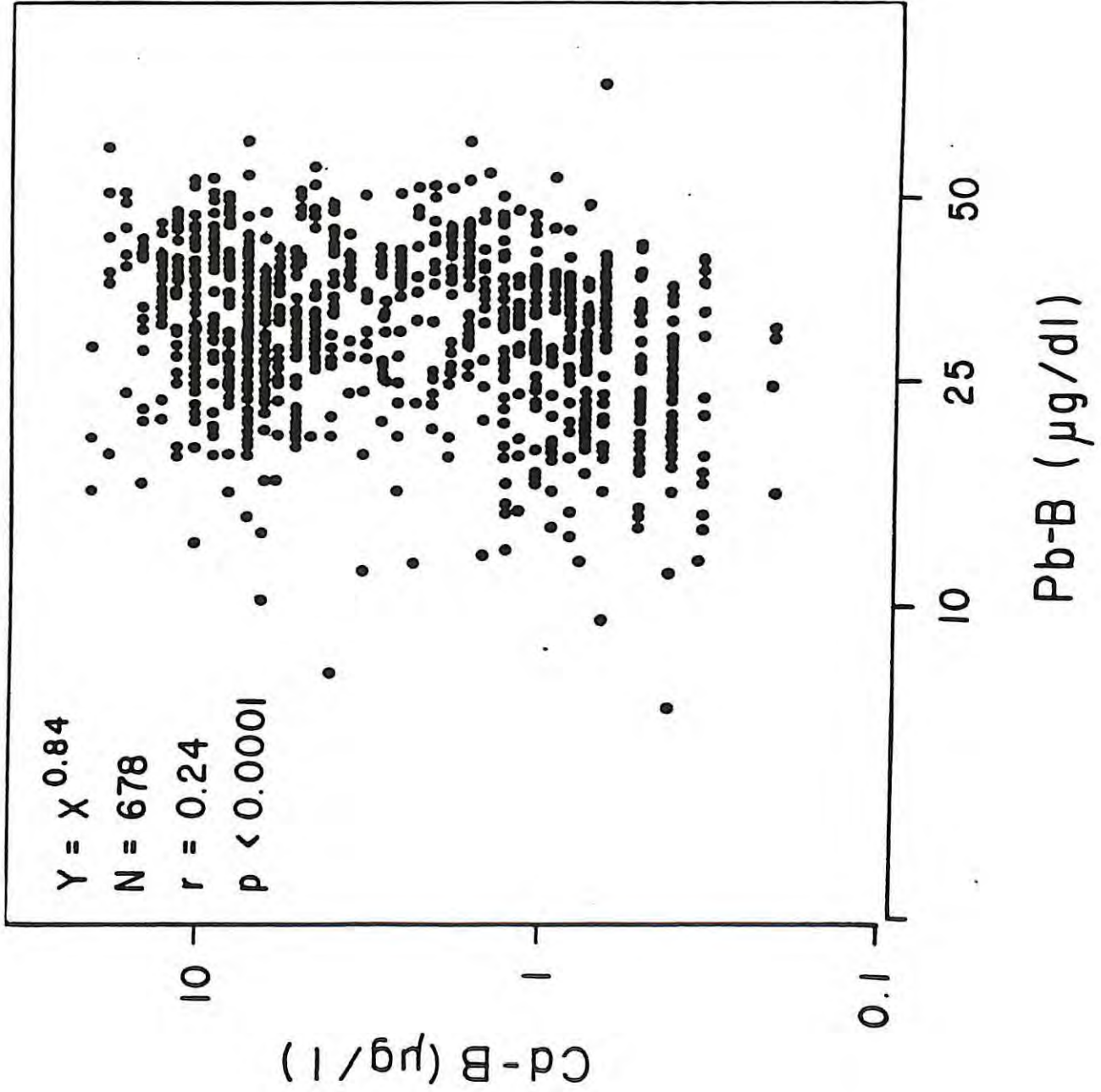


Figure 2 - 5

Active Employees

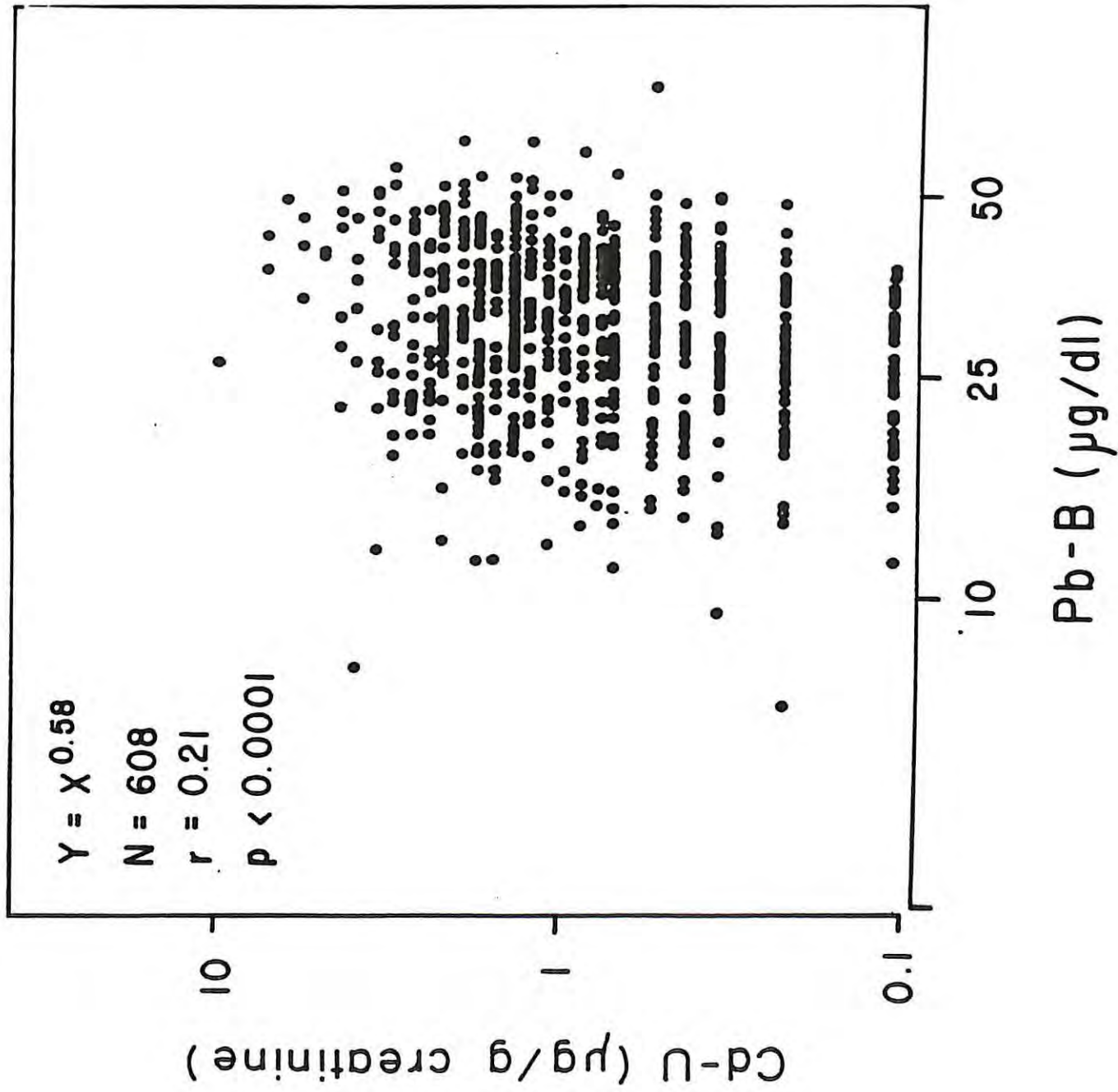


Figure 2 - 6

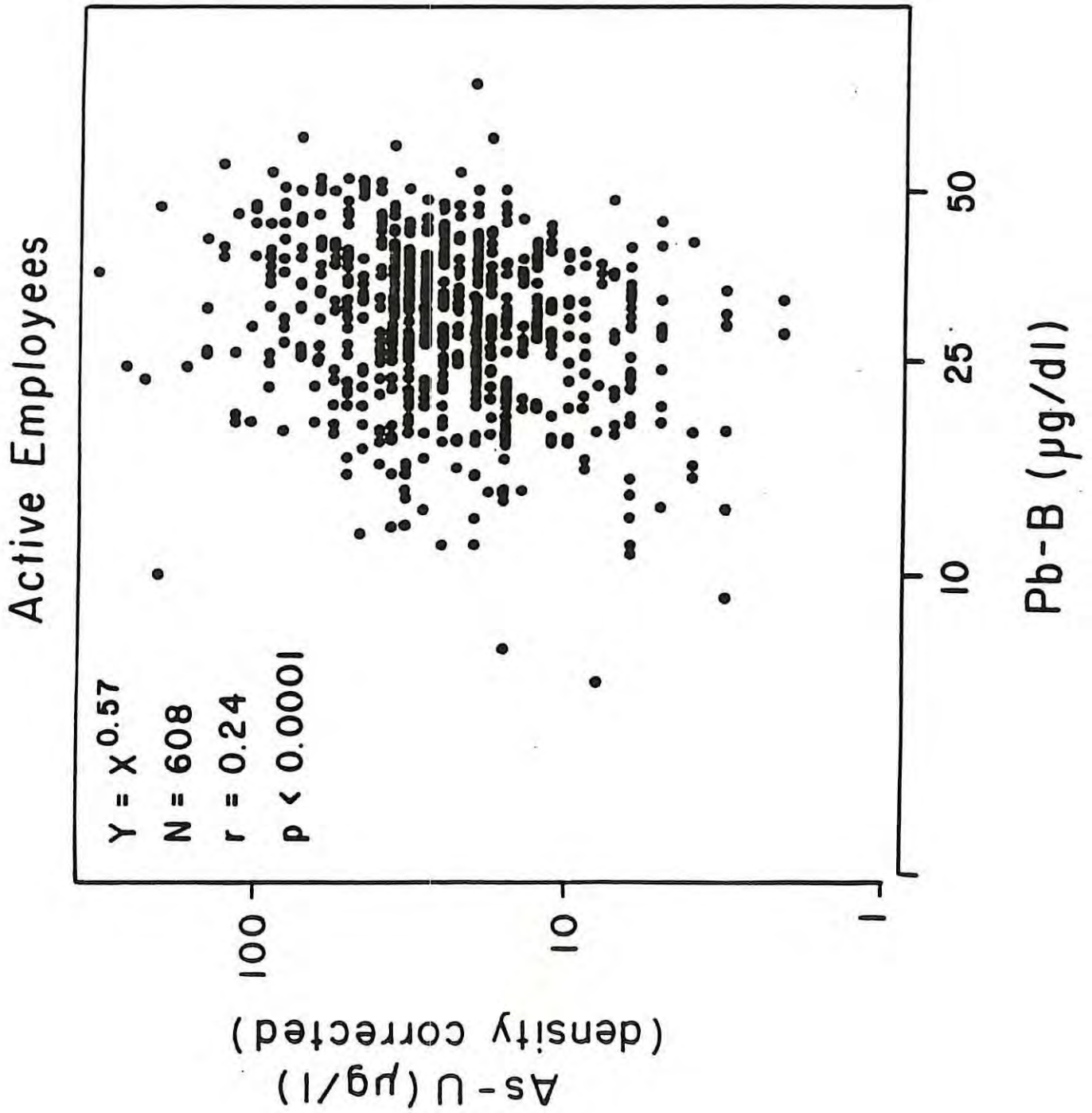


Figure 2 - 7

SMOKING HABITS and Pb-B, Cd-B and As-U
(mean values) in COPPER SMELTER EMPLOYEES

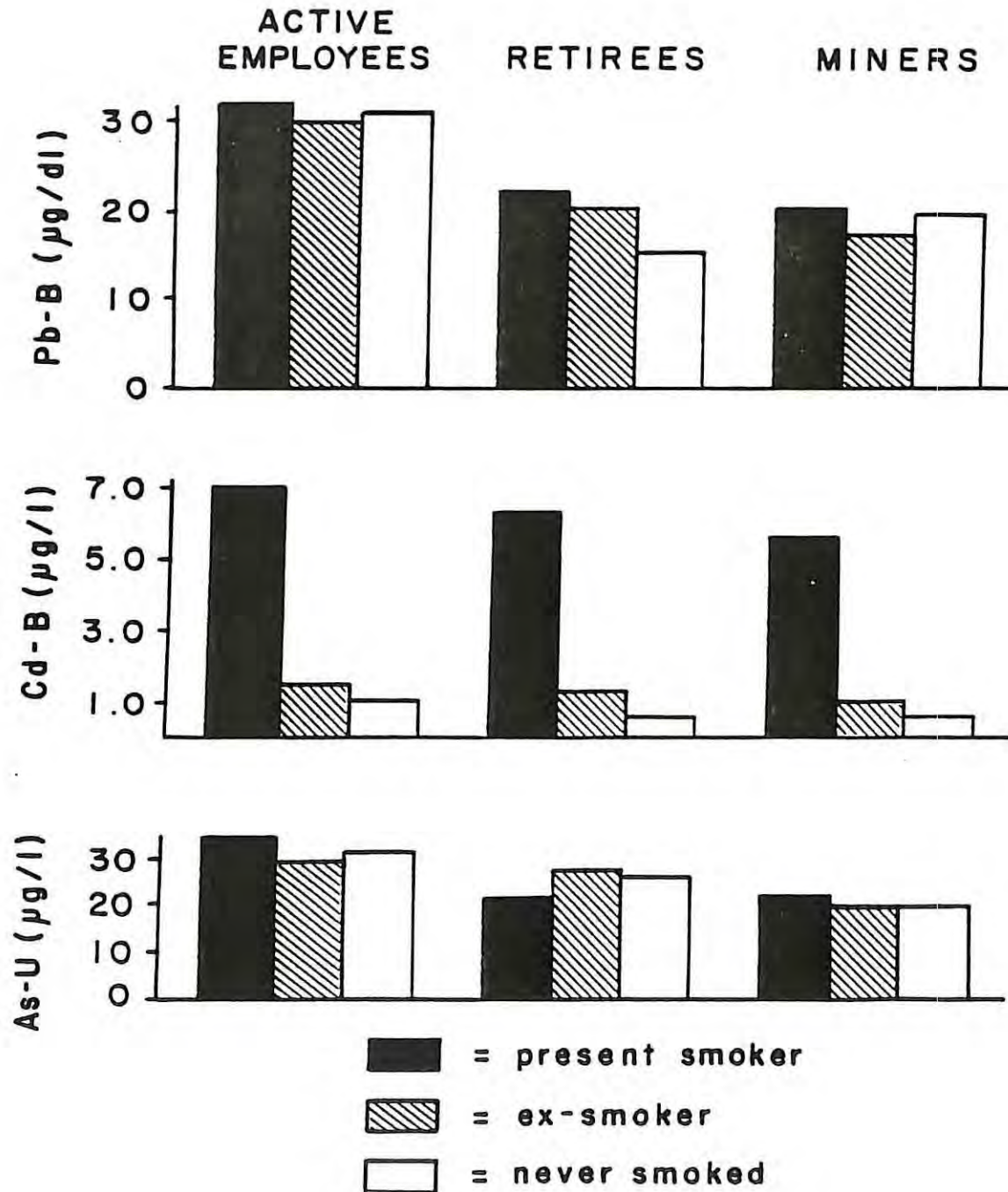


Figure 2 - 8

There was a consistent increase in Cd-B and Cd-U according to increasing intensity of exposure (Table 2-13); this occurred for all three smoking categories (smokers, ex-smokers, non-smokers). These findings clearly indicate that exposure to Cd-containing fumes and dusts, and cigarette smoking can independently contribute to cadmium absorption and elevation of blood and urinary Cd levels. Mallow's Cp criterion for ranking of factors contributing to blood cadmium levels showed that in the order of their respective importance (under circumstances of exposure characteristic for this copper smelter), the factors were: smoking, intensity of exposure, age, and duration of exposure (Table 2-14). When combining the above listed factors, the strongest influence on Cd-B levels was that of intensity of exposure and smoking (for combinations of two) and duration of exposure + intensity of exposure + smoking (for combinations of three). With regard to Cd-U, age was found to be the most important factor (Tables 2-15 and 2-16).

Discussions and Conclusions

The presence and degree of increased absorption of lead, cadmium and arsenic in a copper smelter work force were documented. The Pb absorption was moderate and was in the range in which lead absorption by itself usually does not result in major adverse health effects. The urinary cadmium excretion, while not exceeding the presently accepted "critical" level of 10 µg/g creatinine, was definitely higher than levels found in non-exposed populations.

Moreover, blood cadmium (Cd-B) levels for smokers exceeded those found in the general population by a factor of 2.5-3.5;^{14 15 16} among ex-smokers and non-smokers, median and mean Cd-B did not exceed levels found in the general population, although a gradual increase in median and mean Cd-B from "very low" exposure to "medium" and "high" exposure was present in both ex-smokers and non-smokers.

The differences between Cd-B levels in smokers and non-smokers were much greater in this group of copper smelter workers than differences reported in studies of non-occupationally exposed populations. Most studies on Cd-B levels in the general population have reported median (or geometric mean)

Table 2 - 13

Blood cadmium levels ($\mu\text{g/l}$), intensity of exposure and smoking habits in active copper smelter employees

		Exposure category			
		Very low	Low	Medium	High
Smokers	N	48	102	103	128
	Median	5.03	6.75	7.10	6.90
	Mean \pm SD	5.50 \pm 4.07	6.79 \pm 4.19	7.05 \pm 3.66	7.48 \pm 4.28
Ex-smokers	N	21	55	52	47
	Median	0.70	0.90	1.00	1.40
	Mean \pm SD	0.76 \pm 0.34	1.03 \pm 0.62	1.53 \pm 1.80	1.02 \pm 1.61
Nonsmokers	N	11	35	33	42
	Median	0.50	0.60	0.80	1.00
	Mean \pm SD	0.56 \pm 0.27	0.65 \pm 0.80	0.99 \pm 0.80	1.53 \pm 1.28

Urinary cadmium ($\mu\text{g/g}$ Creatinine), intensity of exposure and smoking habits in active copper smelter employees

		Exposure category			
		Very low	Low	Medium	High
Smokers	N	45	86	87	120
	Median	1.00	1.10	1.20	1.40
	Mean \pm SD	1.23 \pm 0.89	1.21 \pm 0.89	1.45 \pm 1.26	1.65 \pm 1.33
Ex-smokers	N	19	45	48	45
	Median	0.50	0.70	0.70	1.10
	Mean \pm SD	0.69 \pm 0.55	0.98 \pm 0.81	0.88 \pm 0.65	1.20 \pm 0.81
Nonsmokers	N	10	33	29	41
	Median	0.45	0.30	0.40	0.60
	Mean \pm SD	0.50 \pm 0.28	0.41 \pm 0.27	0.62 \pm 0.66	0.72 \pm 0.47

Table 2 - 14

Ranking of factors contributing to blood cadmium levels
Mallows' Cp criterion

	<u>Cp(*)</u>	<u>r-square (**)</u>
Smoking	23.2	0.37
Intensity of exposure	418.9	0.01
Age	431.0	0.006
Duration of exposure	435.3	0.002
Intensity of exposure + smoking	6.0	0.39
Age + smoking	19.5	0.38
Duration of exposure + smoking	20.9	0.38
Duration of exposure + intensity of exposure + smoking	4.21	0.39
Age + intensity of exposure + smoking	4.51	0.39
Age + duration of exposure + smoking	20.2	0.38

(*) "Best" is defined as the smallest Cp.

(**) The contribution to r-square for each variable is the amount by which r-square would be reduced if that variable were removed from the regression equation.

Table 2 - 15

Ranking of factors contributing to urinary cadmium levels
(density corrected)
Mallows' Cp criterion

	<u>Cp(*)</u>	<u>r-square (**)</u>
Age	114.7	0.11
Smoking	123.9	0.09
Duration of exposure	136.0	0.08
Intensity of exposure	185.5	0.02
Age + smoking	38.5	0.20
Duration of exposure + smoking	66.8	0.17
Age + duration of exposure	97.6	0.13
Age + intensity of exposure + smoking	17.9	0.23
Age + duration of exposure + smoking	24.5	0.22
Duration of exposure + intensity of exposure + smoking	53.7	0.19

(*) "Best" is defined as the smallest Cp.

(**) The contribution to r-square for each variable is the amount by which r-square would be reduced if that variable were removed from the regression equation.

Table 2 - 16

Ranking of factors contributing to urinary cadmium levels
(Creatinine corrected)
Mallows' Cp criterion

	<u>Cp(*)</u>	<u>r-square (**)</u>
Age	130.2	0.14
Smoking	163.9	0.10
Duration of exposure	189.2	0.07
Intensity of exposure	234.0	0.02
Age + intensity of exposure	102.6	0.18
Duration of exposure + smoking	107.2	0.17
Age + duration of exposure	120.2	0.16
Age + intensity of exposure + smoking	11.4	0.29
Age + duration of exposure + smoking	32.7	0.26
Duration of exposure + intensity of exposure + smoking	89.1	0.20

(*) "Best" is defined as the smallest Cp.

(**) The contribution to r-square for each variable is the amount by which r-square would be reduced if that variable were removed from the regression equation.

Cd-B levels in smokers to be 1.5 to 3 times higher than in non-smokers. In this study, in active smelter employees, median Cd-B levels in smokers were approximately 10 times higher than in non-smokers (Table 2-13). When comparing median Cd-B in smoking copper smelter employees with Cd-B (geometric mean) reported from a cooperative study on Cd and Pb levels in the general population in 10 different countries,¹⁷ the workers in our study had Cd-B levels 4.5 to 5.5 times higher than were found for smokers in the U.S. For ex-smokers, the geometric mean of Cd-B for the U.S. was 0.8 µg/l while in the copper smelter employees the median Cd-B varied from 0.7 µg/l in subjects with low exposure jobs to 1.4 µg/l in those with relatively high exposure. Similarly, for male non-smokers in the general population the geometric mean for Cd-B was 0.6 µg/l, while for the copper smelter employees it ranged from 0.5 µg/l in the very low exposure group to 1.0 µg/l in the high exposure group.

Consequently, for non-smokers and ex-smokers among the copper smelter employees, blood cadmium was differentially increased above levels found in the general population; for subjects in jobs classified as "high" exposure, an almost two fold increase in median Cd-B was found as compared to the geometric mean in non-smokers or ex-smokers in the general population.

Tables 2-17, 2-18, 2-19, 2-20, 2-21, 2-22 present mean, median and range of Pb-B, ZPP, Cd-B, Cd-U, and As-U in the most important occupations in the copper smelter. The differences among the various occupations are obvious; for each of the metals, a subpopulation with higher absorption can be identified. Preventive engineering controls and medical surveillance should address with priority the subgroups with higher levels of exposure and absorption of Cd, Pb and As.

Table 2 - 17

Blood lead (median, mean \pm SD, and range)
in different job categories of copper
smelter employees

<u>Job categories</u>	<u>Pb-B μg/dl</u>			
	<u>N</u>	<u>Median</u>	<u>Mean \pm SD</u>	<u>Range</u>
RAILROAD CONSTRUCTION YARD	24	22.1	23.0 \pm 8.0	11.8 - 51.3
CONCENTRATOR	25	23.2	23.6 \pm 4.2	15.2 - 31.9
LABORER (OUTSIDE)	21	24.5	25.5 \pm 8.3	11.8 - 41.3
CARPENTER	22	25.0	26.3 \pm 11.3	10.2 - 53.4
POWER HOUSE BOILER	15	25.2	25.2 \pm 5.7	18.2 - 36.4
ELECTRICAL SHOP	36	25.3	25.3 \pm 7.8	11.0 - 46.0
MACHINE SHOP	28	25.6	24.5 \pm 6.5	12.1 - 38.1
ROASTER OR MIXER	16	28.2	28.1 \pm 9.4	12.1 - 43.6
WELDER	18	28.9	32.8 \pm 10.7	19.7 - 49.3
HEAVY EQUIPMENT MAINTENANCE	46	29.0	28.9 \pm 10.0	7.9 - 50.0
PIPEFITTER OR PLUMBER	23	29.6	31.4 \pm 10.0	16.5 - 52.9
CONCENTRATOR UNLOADING SHED	26	30.0	32.0 \pm 9.2	15.2 - 51.9
SAMPLE MILL	32	31.2	28.5 \pm 9.0	11.4 - 40.9
CONVERTOR	72	31.3	30.7 \pm 10.6	12.1 - 62.3
FURNACE	84	32.5	32.4 \pm 10.7	9.5 - 74.8
DUST COLLECTOR	20	36.1	34.9 \pm 10.2	18.9 - 53.6
REACTOR FEEDER	47	38.3	37.2 \pm 9.3	14.4 - 55.1
RIGGER	27	39.6	39.4 \pm 10.9	11.8 - 62.3

Table 2 - 18

Zinc protoporphyrin (median, mean \pm SD, and range)
in different job categories of copper smelter
employees

ZPP $\mu\text{g}/\text{dl}$

<u>Job categories</u>	<u>N</u>	<u>Median</u>	<u>Mean \pm SD</u>	<u>Range</u>
RAILROAD CONSTRUCTION YARD	23	31.0	34.8 \pm 12.7	22.5 - 82.0
CONCENTRATOR	25	34.0	35.5 \pm 8.3	23.5 - 58.5
ELECTRICAL SHOP	36	35.0	42.1 \pm 22.5	24.5 - 125.5
SAMPLE MILL	31	36.0	39.6 \pm 16.7	22.0 - 100.5
MACHINE SHOP	27	37.0	40.0 \pm 10.1	25.0 - 66.0
LABORER (OUTSIDE)	21	37.0	41.4 \pm 11.3	24.5 - 62.5
DUST COLLECTOR	20	37.5	48.1 \pm 29.5	23.5 - 148.5
CARPENTER	21	39.0	50.6 \pm 29.7	21.5 - 124.5
WELDER	19	39.5	54.3 \pm 39.5	28.5 - 198.0
POWER HOUSE BOILER	15	39.5	43.0 \pm 15.3	20.5 - 72.5
CONCENTRATOR UNLOADING SHED	26	42.0	49.1 \pm 21.8	26.0 - 114.0
FURNACE	84	43.2	49.6 \pm 22.0	27.5 - 137.5
ROASTER OR MIXER	16	43.5	46.2 \pm 27.4	27.0 - 144.5
CONVERTOR	72	44.7	53.2 \pm 26.9	21.0 - 154.5
HEAVY EQUIPMENT MAINTENANCE	46	45.0	57.1 \pm 38.8	25.5 - 226.0
PIPEFITTER OR PLUMBER	23	46.0	50.8 \pm 19.3	28.5 - 107.5
REACTOR FEEDER	46	50.5	62.3 \pm 35.7	26.0 - 174.0
RIGGER	27	60.5	68.1 \pm 29.0	33.5 - 143.0

Table 2 - 19

Blood cadmium (median, mean \pm SD, and range)
in different job categories of copper
smelter employees

<u>Job categories</u>	<u>N</u>	<u>Cd-B $\mu\text{g/l}$</u>		
		<u>Median</u>	<u>Mean \pm SD</u>	<u>Range</u>
MACHINE SHOP	28	1.10	2.96 \pm 3.66	0.3 - 15.5
ELECTRICAL SHOP	36	1.20	2.61 \pm 3.00	0.4 - 11.3
LABORER (OUTSIDE)	21	1.40	2.82 \pm 2.69	0.5 - 9.5
RAILROAD CONSTRUCTION YARD	24	1.50	3.62 \pm 4.21	0.3 - 13.5
CONVERTOR	72	1.60	3.80 \pm 3.72	0.3 - 14.3
CARPENTER	22	1.65	3.22 \pm 3.17	0.3 - 9.1
PIPEFITTER OR PLUMBER	23	2.50	4.00 \pm 3.81	0.4 - 12.3
FURNACE	84	2.60	4.33 \pm 4.15	0.1 - 18.1
SAMPLE MILL	32	3.35	5.35 \pm 5.38	0.2 - 21.0
WELDER	18	3.45	4.41 \pm 3.60	1.0 - 14.7
HEAVY EQUIPMENT MAINTENANCE	46	3.50	4.35 \pm 3.89	0.4 - 16.4
ROASTER OR MIXER	16	4.00	4.67 \pm 3.84	0.2 - 13.1
CONCENTRATOR UNLOADING SHED	26	4.20	5.69 \pm 4.79	0.3 - 16.8
REACTOR FEEDER	47	4.50	6.17 \pm 4.68	0.4 - 18.6
CONCENTRATOR	25	4.70	4.84 \pm 4.96	0.2 - 19.4
RIGGER	27	5.20	5.29 \pm 4.23	1.0 - 18.0
DUST COLLECTOR	20	5.60	5.31 \pm 3.71	0.4 - 11.4
POWER HOUSE BOILER	15	6.90	5.98 \pm 4.66	0.4 - 13.4

Table 2 - 20

Urinary cadmium -density corrected (Median, mean \pm SD, and range) in different job categories of copper smelter employees

Cd-U μ g/l (density corrected)

<u>Job categories</u>	<u>N</u>	<u>Median</u>	<u>Mean \pm SD</u>	<u>Range</u>
SAMPLE MILL	25	0.80	1.44 \pm 1.27	0.1 - 4.1
ELECTRICAL SHOP	34	0.85	1.15 \pm 0.99	0.1 - 4.2
CARPENTER	21	1.00	1.94 \pm 1.95	0.1 - 7.3
RAILROAD CONSTRUCTION YARD	21	1.10	1.33 \pm 0.92	0.5 - 4.3
LABORER (OUTSIDE)	19	1.10	1.70 \pm 1.31	0.1 - 4.6
POWER HOUSE BOILER	15	1.10	1.51 \pm 1.42	0.2 - 5.7
CONCENTRATOR	16	1.30	1.67 \pm 1.39	0.2 - 4.9
RIGGER	25	1.30	1.63 \pm 1.11	0.3 - 5.3
PIPEFITTER OR PLUMBER	19	1.40	1.86 \pm 1.56	0.3 - 6.5
CONVERTOR	64	1.40	1.55 \pm 1.23	0.1 - 6.0
MACHINE SHOP	26	1.50	1.82 \pm 1.58	0.3 - 7.8
DUST COLLECTOR	18	1.50	2.29 \pm 2.18	0.3 - 7.6
HEAVY EQUIPMENT MAINTENANCE	44	1.65	2.10 \pm 1.48	0.4 - 5.9
REACTOR FEEDER	42	1.70	2.50 \pm 1.99	0.3 - 8.4
WELDER	14	1.75	2.48 \pm 2.78	0.1 - 11.0
FURNACE	81	1.80	2.91 \pm 3.33	0.1 - 18.1
ROASTER OR MIXER	16	1.90	2.41 \pm 2.47	0.3 - 10.3
CONCENTRATOR UNLOADING SHED	26	2.05	2.03 \pm 1.33	0.2 - 4.9

Table 2 - 21

Urinary cadmium -creatinine corrected (median, mean \pm SD, and range) in different job categories of copper smelter employees

<u>Job categories</u>	<u>Cd-U μg/g creatinine</u>			
	<u>N</u>	<u>Median</u>	<u>Mean \pm SD</u>	<u>Range</u>
SAMPLE MILL	25	0.50	0.92 \pm 0.74	0.1 - 2.4
ELECTRICAL SHOP	34	0.55	0.70 \pm 0.55	0.1 - 1.9
RAILROAD CONSTRUCTION YARD	21	0.70	0.88 \pm 0.61	0.3 - 2.4
CONCENTRATOR	16	0.70	0.99 \pm 0.80	0.1 - 2.6
CARPENTER	21	0.70	1.25 \pm 1.27	0.1 - 5.0
POWER HOUSE BOILER	15	0.80	0.97 \pm 0.73	0.2 - 2.8
MACHINE SHOP	26	0.80	1.12 \pm 0.79	0.2 - 3.3
PIPEFITTER OR PLUMBER	19	0.80	1.09 \pm 0.83	0.2 - 2.6
CONVERTOR	64	0.90	1.08 \pm 1.25	0.1 - 9.4
LABORER (OUTSIDE)	19	1.00	1.10 \pm 0.78	0.1 - 2.9
DUST COLLECTOR	18	1.05	1.33 \pm 1.26	0.2 - 4.9
RIGGER	25	1.10	1.13 \pm 0.81	0.2 - 3.7
HEAVY EQUIPMENT MAINTENANCE	44	1.10	1.34 \pm 0.95	0.2 - 4.4
WELDER	14	1.10	1.32 \pm 1.13	0.1 - 4.2
CONCENTRATOR UNLOADING SHED	26	1.20	1.20 \pm 0.77	0.1 - 2.9
ROASTER OR MIXER	16	1.20	1.39 \pm 1.05	0.2 - 3.8
REACTOR FEEDER	42	1.20	1.61 \pm 1.28	0.2 - 5.3
FURNACE	81	1.40	1.65 \pm 1.51	0.1 - 6.8

Table 2 - 22

Urinary arsenic (median, mean \pm SD, and range)
in different job categories of copper
smelter employees

As-U $\mu\text{g/g}$ creatinine

<u>Job categories</u>	<u>N</u>	<u>Median</u>	<u>Mean \pm SD</u>	<u>Range</u>
CONCENTRATOR UNLOADING SHED	26	14.5	18.6 \pm 12.9	4 - 50
ROASTER OR MIXER	16	17.0	23.4 \pm 19.0	4 - 70
PIPEFITTER OR PLUMBER	19	18.0	28.2 \pm 24.2	7 - 84
CONVERTOR	64	20.5	29.7 \pm 32.7	2 - 18
POWER HOUSE BOILER	15	21.0	24.7 \pm 12.1	10 - 51
CONCENTRATOR	16	22.0	30.0 \pm 27.5	5 - 91
ELECTRICAL SHOP	34	23.0	30.9 \pm 26.3	3 - 108
LABORER (OUTSIDE)	19	23.0	26.1 \pm 15.0	6 - 65
FURNACE	81	24.0	28.3 \pm 21.4	3 - 105
RAILROAD CONSTRUCTION YARD	21	26.0	31.0 \pm 26.7	5 - 98
CARPENTER	21	26.0	29.5 \pm 25.6	3 - 128
HEAVY EQUIPMENT MAINTENANCE	44	27.0	35.4 \pm 23.8	6 - 97
SAMPLE MILL	25	28.0	31.5 \pm 22.9	3 - 86
MACHINE SHOP	26	28.0	33.1 \pm 30.2	2 - 147
DUST COLLECTOR	18	28.5	42.0 \pm 45.0	6 - 197
RIGGER	25	32.0	35.5 \pm 20.7	3 - 83
WELDER	14	41.0	67.3 \pm 53.9	6 - 148
REACTOR FEEDER	42	47.5	58.9 \pm 49.5	6 - 308

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CHAPTER III

Health status of copper smelter employees
and miners

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INTRODUCTION

Medical histories, reported symptoms, objective findings on physical examination, and pertinent biochemical laboratory results were analyzed for active smelter workers, retired smelter workers and miners. Relationships with duration of employment and time from onset of employment were explored; whenever necessary the effect of age was assessed in order to differentiate between the effect of age and that of duration from onset of exposure. Relationships with indicators of absorption for lead, cadmium and arsenic were explored through multiple approaches, in order to identify health effects which might be attributed to these exposures.

Past Medical History

A medical history questionnaire was administered to all examined. The frequency of reported cardiovascular, metabolic, and renal conditions in copper smelter employees (active and retired) and miners is presented in Tables 3-1 and 3-2. The highest frequency of cardiovascular conditions, such as angina and myocardial infarction, was found among retirees; it should be noted that this subgroup included individuals on disability.

Two conditions were reported more frequently by copper smelter employees: hypertension, which was somewhat more frequent among active smelter workers; and kidney stones, more frequently reported by smelter workers (up to age 60).

Since there was potential for arsenic exposure, special attention was given to skin conditions. Table 3-3 presents the frequency of skin conditions as reported by the examinees. Skin cancer had been diagnosed in only 5 copper smelter employees and in one miner. In a study of a random sample of the male population in the state of Michigan,¹ history of skin cancer was reported by 1.7 percent. It can therefore be concluded that skin cancer does not pose a major problem among copper smelter employees at arsenic exposure and absorption levels found in this study population.

Table 3-1

Past medical history
Reported diagnosed conditions in copper smelter employees and miners

	<u>Copper smelter employees</u>						<u>Miners</u>		
	<u>Active</u>			<u>Retired</u>			<u>≤ 40</u>	<u>41 - 60</u>	<u>> 60</u>
	<u>Age</u> <u>≤ 40</u>	<u>41 - 60</u>	<u>> 60</u>	<u>≤ 40</u>	<u>41 - 60</u>	<u>> 60</u>			
<u>Number of cases</u>	304	320	56	9	28	59	13	69	62
Angina	2 (0.7%)	15 (4.7%)	1 (1.8%)	0	6 (21.4%)	5 (8.5%)	0	5 (7.2%)	10 (16.1%)
Myocardial infarction	3 (1.0%)	13 (4.1%)	1 (1.8%)	0	8 (28.6%)	7 (11.9%)	0	4 (5.8%)	11 (17.7%)
Diabetes	2 (0.7%)	19 (5.9%)	2 (3.6%)	1 (11.1%)	2 (7.1%)	6 (10.2%)	0	6 (8.7%)	7 (11.3%)
Gout	0	6 (1.9%)	2 (3.6%)	0	1 (3.6%)	1 (1.7%)	0	2 (2.9%)	5 (8.1%)
Hypertension	16 (5.3%)	43 (13.4%)	13 (23.2%)	0	3 (10.7%)	13 (22.0%)	0	8 (11.6%)	14 (22.6%)
Kidney stones	3 (1.0%)	25 (7.8%)	0	0	3 (10.7%)	6 (10.1%)	0	2 (2.9%)	8 (12.9%)
Kidney disease (kidney stones, infections or non-specified)	15 (4.9%)	37 (11.6%)	1 (1.8%)	0	4 (14.3%)	8 (13.6%)	1 (7.7%)	9 (13.0%)	14 (22.6%)

Table 3 - 2Reported diagnosed conditions
in copper smelter employees(active and retired)

Age	<u>≤ 40</u>		41-60		<u>> 60</u>	
	N = 313		N = 348		N = 115	
	N	%	N	%	N	%
Angina	2	0.6	21	6.0	6	5.2
MI	3	1.0	21	6.0	8	7.0
Diabetes	3	1.0	21	6.0	8	7.0
Gout	0	0	9	2.6	3	2.6
Hypertension	16	5.1	46	13.2	26	22.6
Kidney stones	3	1.0	28	8.0	6	5.2
kidney disease	15	4.8	41	11.8	9	7.8

Table 3-3

Past medical history
positive for skin conditions

	<u>Copper smelter employees</u>		<u>Miners</u>			
	<u>Active</u>		<u>Retired</u>			
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>		
	N = 680		N = 96		N = 144	
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>
Dermatitis	62	(9.1)	12	(12.5)	15	(10.4)
Pigmentation	8	(1.2)	2	(2.1)	3	(2.1)
Skin ulceration and thickening	12	(1.8)	1	(1.0)	2	(1.4)
Eczema	36	(5.3)	6	(6.2)	8	(5.6)
Skin cancer	3	(0.44)	2*	(2.08)	1	(0.69)

* Skin cancer in a random survey of Michigan males 1.7%

Prevalence of symptoms

Questionnaires concerning symptoms were administered by trained interviewers. These questionnaires were administered independently from both the occupational history questionnaires and the physical examinations which were performed by physicians. Questionnaires and physical examination forms designed for computer analysis were used. They had been used and tested in other clinical field studies of lead exposed occupational groups, such as secondary lead smelter and automobile assembly workers.

The group under consideration in the present study had complex exposures to lead, cadmium, arsenic, sulfur dioxide and inorganic dusts. Therefore, appropriate adaptation of the review of symptoms and physical examination were made to address respiratory symptoms (cadmium, SO₂ and inorganic dusts exposure) and skin conditions (arsenic exposure), in addition to neurological, gastrointestinal and musculo-skeletal symptoms.

Prevalence of symptoms among copper smelter employees and miners is presented in Tables 3-4 and 3-5. Since the age distribution in copper smelter employees differed from that of miners, and since age can influence symptoms, the data are presented for three age groups: less than or equal to 40, 41-60 and over 60 years (Table 3-5).

When comparing active copper smelter employees with miners, no difference was found in prevalence rates of reported symptoms. Retired copper smelter workers were not included in this comparison, since some had retired because of disabling conditions. Sleep disturbances, fatigue, joint pain, paresthesia and muscle pain were the most frequent symptoms reported by active copper smelter employees, while joint pain was the most frequent symptom in miners.

Irritability, headache and nausea occurred with higher prevalence in the younger (less than 40 years) copper smelter employees. It is possible that this reflects toxic effects in the younger copper smelter workers. No definite pattern of symptoms related to toxic exposure could otherwise be identified.

Table 3 - 4

Prevalence of symptoms in copper smelter employees
(active and retired) and miners

	<u>Copper smelter employees</u>						<u>Miners</u>		
	<u>Active</u>			<u>Retired</u>			<u>(N = 144)</u>		
	<u>N</u>		<u>%</u>	<u>N</u>		<u>%</u>	<u>N</u>		<u>%</u>
Irritability	159	[6]*	23.5	33	[6]	34.4	48	[6]	33.6
Fatigue	232	[2]	34.3	44	[2]	46.3	62	[3]	43.1
Weakness	77		11.4	20	[9]	20.8	31	[10]	21.7
Sleep disturbance	260	[1]	38.5	48	[1]	50.0	69	[2]	47.9
Depression	62		9.2	11		11.6	21		14.7
Memory problems	122	[9]	18.0	35	[5]	36.5	48	[6]	33.6
Headaches	144	[7]	21.2	24	[8]	25.3	33	[9]	23.1
Paresthesia	190	[4]	28.1	39	[4]	40.6	61	[4]	42.4
Weight loss	131	[8]	19.3	28	[7]	29.2	36	[7]	25.0
Loss of appetite	94		13.8	16	[10]	16.7	22		15.3
Nausea	66		9.9	13		13.6	13		9.2
Abdominal pain	118	[10]	17.4	24	[8]	25.3	35	[8]	24.5
Abdominal pain with constipation	30		4.4	13		13.5	10		7.0
Muscle pain	175	[5]	25.8	28	[7]	29.2	53	[5]	36.8
Joint pain	214	[3]	31.6	43	[3]	44.8	69	[1]	48.2

* Numbers in brackets [] indicate the order of most frequent symptoms.

	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>
"CNS plus" irritability and/or fatigue and/or sleep disturbance	381	56.0	70	72.9	99	68.7
weight and/or appetite loss	180	26.5	35	36.5	44	30.6
"CNS plus" and weight and/or appetite loss	128	18.8	27	28.1	14	24.3
Muscle pain and/or joint pain	303	44.6	52	54.2	92	63.9

Table 3 - 5

Prevalence of symptoms in copper smelter employees and in miners
(three age groups)

Age (years)	Copper smelter employees (Active)						Miners					
	≤ 40		41 - 60		> 60		≤ 40		41 - 60		> 60	
	N = 304		N = 320		N = 56		N = 13		N = 69		N = 62	
	N	%	N	%	N	%	N	%	N	%	N	%
Irritability	75	25	74	23	10	18	5	38	28	41	15	31
Fatigue	90	30	124	39	18	32	5	38	32	46	25	40
Weakness	23	8	46	15	8	15	1	8	17	25	13	21
Sleep disturbances	105	35	135	42	20	36	5	38	28	41	36	58
Depression	24	8	34	11	4	7	1	8	11	16	9	15
Memory problems	30	10	71	22	21	38	2	15	22	32	24	39
Headaches	79	26	58	18	7	12	1	8	16	23	16	26
Paresthesia	68	22	101	32	21	38	5	38	36	52	20	32
Weight loss	53	17	66	21	12	21	6	46	16	23	14	23
Loss of appetite	42	14	42	13	10	18	1	8	13	19	8	13
Nausea	34	11	30	10	3	4	2	17	6	9	5	8
Abdominal pain	50	16	64	20	4	7	2	17	18	26	15	24
Abdominal pain with constipation	14	5	41	4	2	4	3	23	4	6	3	5
Muscle pain	62	20	93	29	20	36	4	31	31	45	18	29
Joint pain	63	21	124	39	27	48	3	23	33	48	33	54
"CNS plus"	163	54	185	58	33	59	8	62	49	71	42	68
Weight loss and/or appetite loss	80	26	83	26	17	30	6	46	21	30	17	27
"CNS plus" and weight and/or appetite loss	50	16	63	20	15	27	4	31	17	25	14	23
Muscle and/or joint pain	101	33	166	52	36	64	6	46	45	49	41	45

When comparing the prevalence of symptoms among active copper smelter employees with that found in a group of autobody shop employees exposed to lead only, similar prevalence rates were found for most symptoms.² Sleep disturbances, weight loss and muscle pain were the only symptoms with slightly higher prevalence rates in copper smelter employees (Table 3-6).

On the other hand, fatigue, depression, memory problems, loss of appetite, and abdominal pain occurred more frequently among autobody shop employees. Mean age was shifted towards the younger age group in automobile assembly workers (Table 3-7). The autobody shop workers had higher Pb-B levels (Table 3-8).

The fact that the prevalence of reported symptoms was generally similar in copper smelter and automobile assembly employees (although lead absorption was higher in automobile assembly workers) could be related to two factors: older age of copper smelter employees and the presence of other toxic exposures, such as arsenic and cadmium, in addition to lead exposure in the smelter.

Respiratory symptoms

The MRC questionnaire on respiratory symptoms was administered to all examined persons. The prevalence of chronic bronchitis, as defined by the MRC Criteria, is shown in Table 3-9. As expected, chronic bronchitis was more frequent among smokers and ex-smokers in all subgroups. It is of interest to note that chronic bronchitis was found in over 8 percent of copper smelter workers who had never smoked; this is probably related to exposure to irritant gases, fumes and dusts in the smelter environment. Miners had the highest prevalence rates for chronic bronchitis. Twenty-eight percent of the non-smokers (never smoked) had chronic bronchitis, only slightly less than the 36 percent among current smokers. These findings suggest that exposure to dust and irritants in the mining operations contributes significantly to the high prevalence of chronic bronchitis in metal ore miners.

Prevalence rates for chronic, non-productive cough were also investigated and the results are presented in Table 3-10. Of copper smelter employees

Table 3 - 6

Prevalence of symptoms
Comparison of lead-exposed autobody shop employees with
copper smelter workers

	<u>Automobile assembly workers</u>		<u>Active copper smelter workers</u>	
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>
Irritability	58	24	159	23.5
Fatigue	87	36	232	34.3
Sleep disturbances	77	32	260	38.5
Depression	35	14	62	9.2
Memory problems	50	20	122	18.0
"CNS plus"	126	52	381	56.0
Weight loss	37	15	131	19.3
Loss of appetite	45	18	94	13.8
Weight loss and/or loss of appetite	65	27	180	26.5
Abdominal pain	60	25	118	17.4
Abdominal pain with constipation	9	4	30	4.4
"CNS plus" and weight and/or appetite loss	49	20	128	18.8
Muscle pain	49	20	175	25.8
Joint pain	77	32	214	31.6
Muscle and/or joint pain	99	41	303	44.6

Table 3 - 7

Comparative age distribution in copper smelter employees
and automobile assembly (body shop) employees

Age (years)	Copper smelter workers (active) N = 680		Automobile assembly workers N = 244	
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>
< 30	143	21	86	35
30 - 50	293	43.1	86	35
> 50	244	35.8	72	30

Table 3 - 8

Comparative distribution of blood lead (Pb-B) levels in
copper smelter and automobile assembly workers

<u>Blood lead (ug/dl)</u>	<u>Autobody shop employees</u>		<u>Copper smelter employees</u>	
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>
< 40	92	38	566	83.2
40 - 59	108	44	111	16.3
<u>≥ 60</u>	44	18	3	0.4

Table 3 - 9

Prevalence of chronic bronchitis in
copper smelter employees and miners
by history - MRC criteria

	<u>Copper smelter employees</u>						<u>Miners</u>		
	<u>Active</u>			<u>Retired</u>					
	<u>total no.</u>	<u>N</u>	<u>%</u>	<u>total no.</u>	<u>N</u>	<u>%</u>	<u>total no.</u>	<u>N</u>	<u>%</u>
Present smokers	382	98	25.6	43	14	32.6	74	27	36.5
Ex-smokers	175	22	12.6	41	16	39.0	49	11	22.4
Never smoked	122	10	8.2	12	1	8.3	21	6	28.6

Table 3 - 10

Prevalence of chronic cough (non-productive)
in copper smelter employees and miners

	<u>Copper smelter employees</u>						<u>Miners</u>		
	<u>Active</u>			<u>Retired</u>					
	<u>total</u> <u>no.</u>	<u>N</u>	<u>%</u>	<u>total</u> <u>no.</u>	<u>N</u>	<u>%</u>	<u>total</u> <u>no.</u>	<u>N</u>	<u>%</u>
Present smokers	382	56	14.7	43	9	20.9	74	8	10.8
Ex-smokers	175	7	4.0	41	4	9.8	49	4	8.2
Never smoked	122	8	6.6	12	0	-	21	2	9.5

who had never smoked, 6.6 percent reported chronic non-productive cough. Thus, 15 percent of non-smoking copper smelter employees reported respiratory symptoms (cough with or without sputum production). This may indicate etiologic agents in the occupational environment, including irritant gases, fumes and dusts.

Dyspnea on exertion (grades I, II, III and total) was reported more frequently, as expected, by smokers and ex-smokers. In the subgroup of 121 active copper smelter workers who had never smoked, the total prevalence of dyspnea on exertion was 38 percent; 9 percent had grade II and 3 percent grade III dyspnea. Grade II or higher grade dyspnea was thus reported by less than 10 percent of active workers.

Among retired workers who had never smoked, 4 out of 12 (33 percent) had dyspnea on exertion grade II or higher. Among the miners a different pattern of dyspnea on exertion was observed. First, there was no evidence of smoking effect, i.e., dyspnea was not reported more frequently by smokers and ex-smokers than by those who had never smoked. Secondly, prevalence rates for all grades of dyspnea were higher in miners than in active copper smelter employees. The differences were most striking in non-smokers (Table 3-11).

These findings indicate that respiratory dysfunction as reflected by dyspnea on exertion was more common among miners than among copper smelter employees. Two factors should be considered in interpreting these results. Firstly, exposure to silica, other dusts, and irritant fumes in the mining environment probably has a greater adverse effect on respiratory function than have exposures in the copper smelter environment. Secondly, the age of the miners was generally higher than the age of copper smelter employees.

Physical Examination

Evaluation of the workers' general appearance showed that less than 10 percent were underweight. However, 28 percent of active smelter employees and over one-third of miners were overweight (Table 3-12).

Table 3 - 11

Prevalence of dyspnoea on exertion in copper smelter employees and miners

	<u>Copper smelter employees</u>										<u>Miners</u>					
	<u>Total number</u>	<u>Active employees</u> <u>Dyspnoea on exertion</u>				<u>N</u>	<u>Retired employees</u> <u>Dyspnoea on exertion</u>				<u>Total</u>	<u>N</u>	<u>Dyspnoea on exertion</u>			
		<u>I</u>	<u>II</u>	<u>III</u>	<u>Total</u>		<u>I</u>	<u>II</u>	<u>III</u>	<u>Total</u>			<u>I</u>	<u>II</u>	<u>III</u>	<u>Total</u>
Present Smokers	380	196 (51.3%)	55 (14.4%)	24 (6.3%)	199 (52.4%)	43	35 (81.4%)	17 (39.5%)	14 (32.6%)	35 (81.4%)	74	57 (77.0%)	33 (44.6%)	24 (32.4%)	57 (77.0%)	
Ex-smokers	174	71 (40.6%)	27 (15.4%)	9 (5.2%)	72 (41.4%)	41	30 (73.2%)	19 (46.3%)	14 (34.1%)	30 (73.2%)	49	36 (73.5%)	18 (36.7%)	14 (28.6%)	36 (73.5%)	
Never Smoked	121	46 (37.7%)	11 (9.0%)	4 (3.3%)	46 (38.0%)	12	8 (66.7%)	4 (33.3%)	2 (16.7%)	8 (66.7%)	21	19 (90.5%)	12 (57.1%)	14 (66.7%)	19 (90.5%)	

Shortness of breath:

- I Walking uphill or climbing stairs
- II Compared with peers
- III On level ground, at own pace

Table 3 - 12

General appearance on physical examination

Age	<u>Copper smelter employees</u>						<u>Miners</u>						
	Total no.	<u>Active</u>		Total no.	<u>Retired</u>		Total no.	Under-weight		Over-weight			
		Under-weight	Over-weight		Under-weight	Over-weight		Under-weight	Over-weight				
		<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>		
≤ 40	304	9	(2.8)	44	(14.5)	9	0	4	(44.4)	13	0	1	(7.7)
41 - 60	320	11	(3.4)	89	(27.8)	28	4	11	(39.3)	69	5	29	(42.0)
> 60	56	3	(5.4)	16	(28.6)	59	2	20	(33.9)	62	6	20	(32.3)

The results of chest examination are presented in Table 3-13. For both groups of workers, the effect of smoking was obvious. However, the prevalence rates of abnormalities, such as increased A-P diameter, hyperresonance, decreased breath sounds, the second pulmonic sound being louder than the aortic on cardiac auscultation (IIP > IIA) were higher in miners than in active copper smelter employees; the highest prevalence of abnormalities was detected in retired copper smelter workers. Because of the small number of non-smokers among retired copper smelter employees and miners meaningful comparisons were not feasible.

Clubbing was detected in 36 active and 9 retired smelter employees and in 20 miners; the prevalence was highest in miners. In all groups, ex-smokers had the highest prevalence of clubbing (Table 3-14).

Arrhythmia was detected in 13 copper smelter employees and in 6 miners. Arrhythmia was twice as prevalent in miners than in all copper smelter workers (active and retired). Skin abnormalities were not prominent on physical examination (Table 3-15).

Neurological examinations focused on impairment of motor and/or sensory peripheral nerve function because of potential effects of arsenic and lead exposures. Special neurophysiologic and behavioral tests were also performed and their correlation with Pb-B and ZPP levels analyzed (Chapters IV-VI).

None of the workers had clinically overt peripheral neuropathy i.e., with significant decrease in muscle strength, muscle hypotrophy and/or obvious sensory loss. Prevalence of abnormalities in deep tendon reflexes and touch and pain sensation was similar in both copper smelter employees and in miners (Table 3-16). Nutritional factors, diabetes, and osteoarthritis must be considered in the interpretation of such peripheral nervous system changes.

Emphysema

Since a number of investigators have reported higher incidence of emphysema in workers with long-term cadmium exposure, evaluation of pulmonary effects

Table 3-13

Objective findings on chest examinations of copper smelter employees and miners

	Copper smelter employees						Miners		
	Active			Retirees			Current smokers N=74	Ex-smokers N=49	Never smoked N=21
	Current smokers N=382	Ex-smokers N=175	Never smoked N=122	Current smokers N=43	Ex-smokers N=41	Never smoked N=12			
Increased A-P diameter	36 (9.4%)	14 (8.0%)	6 (4.9%)	15 (34.9%)	11 (26.8%)	0	20 (27.0%)	11 (22.4%)	4 (19.0%)
Hyperresonance	29 (6.3%)	5 (2.9%)	2 (1.6%)	10 (23.3%)	11 (26.8%)	0	12 (16.2%)	7 (14.3%)	0
Decreased breath sounds	31 (8.1%)	8 (4.6%)	1 (0.8%)	10 (23.3%)	10 (24.4%)	1 (8.3%)	12 (16.2%)	7 (14.3%)	2 (9.5%)
Wheezing and/or rhonchi	56 (14.7%)	9 (5.1%)	4 (3.3%)	15 (34.9%)	7 (17.1%)	0	17 (23.0%)	10 (20.4%)	2 (9.5%)
Lengthening expiratory phase	31 (8.1%)	8 (4.6%)	1 (0.8%)	7 (16.3%)	8 (19.5%)	0	15 (20.3%)	12 (24.5%)	0
PII > AII	7 (1.8%)	2 (1.1%)	2 (1.6%)	4 (9.3%)	6 (14.6%)	0	1 (1.3%)	3 (6.1%)	0

Table 3 - 14

Clubbing in copper smelter employees and miners

	<u>Copper smelter employees</u>						<u>Miners</u>											
	<u>Active</u>			<u>Retired</u>														
	<u>Current smokers</u>	<u>Ex-smokers</u>	<u>Never smoked</u>	<u>Current smokers</u>	<u>Ex-smokers</u>	<u>Never smoked</u>	<u>Current smokers</u>	<u>Ex-smokers</u>	<u>Never smoked</u>	<u>Current smokers</u>	<u>Ex-smokers</u>	<u>Never smoked</u>						
	N = 382		N = 175		N = 122		N = 43		N = 41		N = 12		N = 74		N = 49		N = 21	
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>
Clubbing	20	5.2	14	8.0	2	1.6	4	9.3	5	12.2	0	-	12	16.2	6	12.2	2	9.6

Table 3 - 15

Skin abnormalities on physical examination of
copper smelter employees and miners

	<u>Copper smelter employees</u>				<u>Miners</u>	
	<u>Active</u>		<u>Retired</u>		N = 144	
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>
Rash	13	1.9	4	4.2	4	2.8
Eczema	7	1.0	1	1.0	0	-

Table 3 - 16

Neurologic findings in copper smelter employees
and miners

	<u>Copper smelter employees</u>				<u>Miners</u>	
	<u>Active</u>		<u>Retired</u>		N = 144	
	N = 680		N = 96			
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>
Tremor	59	8.7	19	19.8	19	13.2
Deep tendon reflex abnormalities						
<u>Absent</u>	29	4.3	12	12.5	14	9.7
<u>Decreased</u>	53	7.8	13	13.5	18	12.5
Distal sensory (touch, pain) hypoesthesia	26	3.8	8	8.3	16	11.1

and their relationship to cadmium exposure in this study population was of particular interest. Standard size (14" x 17") chest X-ray films were interpreted according to the International Classification of Radiographs of Pneumoconioses. Radiological evidence of emphysema was present in 60 (9%) copper smelter workers. Since employment in the copper smelter was characterized by complex exposures, (including SO₂, dusts and fumes), and since other factors, such as age and smoking influence the development of emphysema, an attempt to evaluate cadmium as an etiological factor had to take into account the multiple other factors which could affect the outcome.

Mallow's Cp Criterion for ranking of factors contributing to radiologic evidence of emphysema was applied for both active and retired smelter employees as well as for miners (Tables 3-17, 3-18, and 3-19). For smelter employees, both active and retired, urinary cadmium had the highest rank among factors contributing to emphysema; for miners age ranked highest.

Pulmonary function test results and their relationship with exposures in the copper smelter, including cadmium exposure, were analyzed and are reported separately (Chapters VII and VIII).

Radiologic evidence of emphysema was detected in 30 (20.8%) of examined miners. This was not unexpected for two reasons: 1) Prevalence of small, rounded opacities, characteristic of silicosis, was higher in miners and emphysema is a very frequent finding associated with silicosis; 2) Miners were older than the copper smelter workers.

When comparing the age of copper smelter workers with radiologic evidence of emphysema with that of miners with similar findings, it was found that the difference was statistically significant. Mean age for copper smelter workers was 55.6 vs. 61.6 for miners ($t = 2.10$, $p = 0.04$); mean age for active copper smelter workers with radiologic signs of emphysema 52.2; $t = 3.33$, $p = 0.0014$. Thus, the data suggest that radiologic evidence of emphysema can be detected at significantly younger ages in copper smelter workers than in miners without smelter experience; the contribution of cadmium exposure is strongly suggested by the result of Mallow's test.

Table 3 - 17Ranking of factors contributing to radiologic evidence of emphysema in active copper smelter workers

<u>Mallows' Cp Criterion</u>		
	Cp [*]	r-square
Cdu	14.18	0.06
Age	24.33	0.04
Pack-years cigarette smoking	36.01	0.02
CdB	37.95	0.01
Duration of smelter employment	44.59	0.00
Age + CdU	8.28	0.07
CdU + Pack-years	14.39	0.06
Duration of smelter employment + CdU	14.63	0.06
CdB + CdU	15.48	0.06
Duration of smelter employment + Age + CdU	4.10	0.09
Age + CdB + CdU	7.51	0.08
Age + CdU + Pack- years	10.23	0.07

*Best is defined as the smallest Cp.

**The contribution to r-square for each variable is the amount by which r-square would be reduced if that variable were removed from the regression equation.

Table 3 - 18Ranking of factors contributing to radiologic evidence of emphysema in retired copper smelter workers

	<u>Mallows' Cp Criterion</u>	
	<u>Cp</u> [*]	<u>r-square</u>
CdU	1.57	0.15
CdB	10.89	0.03
Age	11.74	0.02
Duration of copper smelter employment	11.96	0.02
Pack-years cigarette smoking	12.20	0.01
Duration of copper smelter employment + CdU	0.95	0.19
Age + CdU	1.71	0.18
CdU + Pack-years	3.50	0.15
CdB + CdU	3.57	0.15
Duration of copper smelter employment + Age + CdU	2.61	0.19
Duration of copper smelter employment + CdU + Pack-years	2.67	0.19

*"Best" is defined as the smallest Cp.

**The contribution to r-square for each variable is the amount by which r-square would be reduced if that variable were removed from the regression equation.

Table 3 - 19

Ranking of factors contributing to radiologic evidence of emphysema
in miners

<u>Mallows' Cp Criterion</u>		
	Cp *	r-square **
Age	4.05	0.03
CdB	5.19	0.02
Pack-years cigarette smoking	6.52	0.01
CdU	7.28	0.00
Age + CdB	1.65	0.07
Age + Pack-years	5.74	0.03
Age + CdU	5.83	0.03
CdU + Pack-years	8.42	0.01
Age + CdB + Pack-years	3.01	0.08
Age + CdB + CdU	3.65	0.07

* "Best" is defined as the smallest Cp.

** The contribution to r-square for each variable is the amount by which r-square would be reduced if that variable were removed from the regression equation.

Hypertension

Hypertension was of special interest in this group of copper smelter workers, since both lead and cadmium have been considered to be potentially related to hypertension. In a previous study of an occupationally lead-exposed group (automobile assembly body shop workers) significantly higher diastolic blood pressure than in a comparison group without lead exposure was documented.¹ Although the level of lead absorption in the present study group - as reflected in blood lead and zinc protoporphyrin levels - is lower than that among the automobile assembly (body shop) employees, the copper smelter employees are also exposed to cadmium. Therefore, the possibility that hypertension could occur with higher frequency was investigated.

Prevalence rates for hypertension (systolic and diastolic) in copper smelter employees and miners, by age group, are presented in Table 3-20. No significant differences were found between copper smelter employees and miners in any of the age categories. When compared to the autobody shop employees, the prevalence rates of diastolic hypertension in copper smelter employees were lower than the corresponding rates for automobile assembly workers and similar to those observed in a general population sample. Since hypertension is known to be more prevalent in blacks than in whites, only white males in the autobody shop were compared with the copper smelter employees, who were all white. Only in the age group over 50 years was the prevalence rate of diastolic hypertension higher than in the general population sample. This was also found among the miners and could not therefore be related to exposures in the smelter only.

Blood pressure (both systolic and diastolic) was found, as expected, to be significantly correlated with age in copper smelter employees and miners; the correlations were consistently higher in copper smelter employees. Significant correlations between blood pressure and Cd-U $\mu\text{g/g}$ creatinine, were found for the smelter workers; no such correlations were detected for miners (Table 3-21). These findings tend to indicate that cadmium absorption and body burden, as reflected in urinary cadmium, might contribute to the incidence of hypertension in copper smelter employees. The fact that both are correlated with age should also be recognized.

Table 3 - 20

Prevalence of hypertension (systolic > 150 mm Hg, diastolic > 95 mm Hg)
in copper smelter employees and in miners

Age (in years)	<u>Copper smelter employees</u>				<u>Miners</u>					
	N	systolic > 150 mm Hg		diastolic > 95 mm Hg		N	systolic > 150 mm Hg		diastolic > 95 mm Hg	
		<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>		<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>
< 30	131	6	4.6	4	3.0	4	0	-	0	-
30 - 50	319	24	7.5	23	7.2	25	2	8.0	3	12.0
> 50	326	97	29.7	49	15.0	115	38	33.0	21	18.3

Table 3 - 21

Correlations between blood pressure (systolic and diastolic),
age, and urinary Cadmium excretion in copper smelter
employees and miners

	<u>Copper smelter employees</u>				<u>Miners</u>	
	Total (active and retired)		Active employees only		systolic	diastolic
	systolic	diastolic	systolic	diastolic		
Age	r = 0.411 p < 0.000001	r = 0.288 p < 0.000001	r = 0.376 p < 0.000001	r = 0.280 p < 0.000001	r = 0.346 p = 0.00001	r = 0.179 p = 0.016
CdU µg/g Creat	r = 0.145 p = 0.00006	r = 0.075 p = 0.025	r = 0.151 p < 0.000001	r = 0.105 p = 0.0048	r = -0.119 p = 0.092	r = -0.114 p = 0.102
log CdU	r = 0.150 p = 0.00004	r = 0.094 p = 0.007	r = 0.148 p = 0.00013	r = 0.123 p = 0.001	n.s. r = -0.082 p = 0.182	n.s. r = -0.09 p = 0.158

The relative importance of several factors with potential contribution to hypertension was also investigated. These factors are: age, an index of body weight versus height (Quetelet Index), duration of employment in the smelter, cadmium absorption and body burden as reflected by Cd-B and Cd-U, and lead absorption as reflected by zinc protoporphyrin.

Based on Mallow's Cp Criterion, it was found that age and body weight had a greater contribution to hypertension, than Cd-B, Cd-U and ZPP.

Renal effects

Potential adverse effects of cadmium on the kidney were of particular interest. Excessive cadmium absorption has been associated with nephropathy, characterized by an increase in the excretion of low molecular weight proteins (typically β -2 microglobulin), due to renal tubular dysfunction. Impairment of the proximal tubular segment of the nephron prevents the normal reabsorption of low molecular weight proteins from the glomerular filtrate. More recently, impairment of glomerular function has also been detected with reduction of glomerular filtration rate and an increase in serum creatinine.³

Renal function in this study group was evaluated by blood urea nitrogen, serum creatinine, and uric acid measurements; urinary excretion of β -2 microglobulin was also assessed. β -2 microglobulin in urine was determined by a radiological method using a commercially available kit (Phadebas 2-micro Test, Pharmacia diagnostics). Phadebas reference serum was run with each group of samples tested.⁴

As previously mentioned, copper smelter workers had evidence of mild to moderate lead absorption. Cadmium absorption and body burden, as reflected by Cd-B and Cd-U, was moderate; Cd-U did not exceed 10 μ g/g creatinine which is considered the "critical level" for renal function impairment. Although both lead and cadmium absorptions were relatively lower than in other occupational groups with well documented renal function impairment due to the effect of the individual metals,⁵ the possibility that simultaneous exposure to these metals could result in renal dysfunction even at lower levels of absorption was considered.

Distribution of blood urea nitrogen (BUN) levels in copper smelter employees was unremarkable (Table 3-22), with relatively few (3.4 percent) elevated values (BUN higher than 26 mg/dl). A similar pattern was found for serum creatinine (Table 3-23); levels of 1.4 mg/dl or higher were found in 3.6 percent of those examined.

Creatinine has not been found to correlate with age in populations without exposure to nephrotoxic agents.^{6 7} In previous studies of lead-exposed groups,^{1 8} significant, positive correlations between serum creatinine, duration of lead exposure, and age were repeatedly found; the degree of these correlations was higher in occupational groups with higher levels of lead absorption. In this group of copper smelter employees, significant correlations between serum creatinine and age, duration of employment and urinary cadmium were found (Table 3-24).

Since the distribution of urinary β -2 microglobulin levels was skewed (Tables 3-25, 3-26) a logarithmic transformation was used in the analysis of data. Means, standard deviations, medians, and ranges for urinary β -2 microglobulin levels are presented in Table 3-27. Cases with clinically established chronic renal conditions, hypertension and/or diabetes were excluded from the analysis.

The possible relationships between urinary β -2 microglobulin levels and Cd-U, Cd-B, Pb-B and ZPP were explored; no significant correlations were detected in either copper smelter employees or miners. There were no significant correlations between urinary β -2 microglobulin excretion and serum creatinine or BUN levels.

However, urinary β -2 microglobulin levels correlated significantly with age in copper smelter employees, but not in miners (Table 3-28). This indicated that long-term exposure in the copper smelter might result in higher levels of β -2 microglobulin. Although age has been found in other studies⁹ to be associated with urinary β -2 microglobulin levels, such a relationship was not found for the miners in this study. Among the active copper smelter workers, a younger group than the miners, a highly significant correlation between urinary β -2 microglobulin excretion and age was present which

Table 3 - 22

Blood urea nitrogen in copper smelter employees
and miners

<u>Blood Urea Nitrogen</u> <u>mg/dl</u>	<u>Copper smelter employees</u>				<u>Miners</u>	
	<u>Active</u>		<u>Retired</u>			
	N = 602		N = 72		N = 117	
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>
< 24	546	90.7	60	83.3	97	82.9
24 - 26	38	6.3	7	9.7	7	6.0
> 26	18	3.0	5	6.9	13	11.1

Table 3 - 23

Serum creatinine in copper smelter employees
and miners

<u>Creatinine mg/dl</u>	<u>Copper smelter employees</u>		<u>Miners</u>			
	<u>Active</u> N = 677	<u>Retired</u> N = 95	N = 142			
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>
< 1.3	630	93.1	86	90.5	119	83.8
1.3 - 1.39	25	3.7	2	2.1	9	6.3
<u>≥ 1.4</u>	22	3.3	7	7.4	14	9.9

Table 3 - 24

Correlations between serum creatinine and age,
duration of smelter employment and urinary
cadmium in active smelter employees

<u>Creatinine mg/dl</u>	<u>Age (years)</u>	<u>Duration of smelter employment</u>	<u>CdU (density corrected)</u>
	r = 0.165	r = 0.131	r = 0.113
	p = 0.00001	p = 0.0003	p = 0.0027

Table 3 - 25

Urinary beta-2 microglobulin levels ($\mu\text{g}/1$ density corrected)
in copper smelter employees and miners

<u>β-2 microglobulins ($\mu\text{g}/1$)</u>	<u>Copper smelter employees</u>		<u>Miners</u>	
	(N = 773)		(N = 140)	
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>
< 200	694	89.8	118	84.3
200 - 399	61	7.9	18	12.9
400 - 999	15	1.9	2	1.4
<u>\geq 1000</u>	3	.4	2	1.4

Table 3 - 26

Urinary beta-2 microglobulin levels ($\mu\text{g/g}$ creatinine)
in copper smelter employees and miners

β -2 microglobulins <u>$\mu\text{g/g}$ creatinine</u>	<u>Copper smelter employees</u>		<u>Miners</u>	
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>
> 200	734	95.0	129	92.2
200 - 399	30	3.9	8	5.7
400 - 999	8	1.0	2	1.4
<u>\geq 1000</u>	1	.1	1	.7

Table 3 - 27

Urinary beta-2 microglobulin levels ($\mu\text{g/g}$ creatinine)
in copper smelter employees and miners

<u>Urinary β-2 microglobulins</u>	<u>Copper smelter employees</u>				<u>Miners</u>	
	<u>Active</u> (N = 560)		<u>Retired</u> (N = 78)		(N = 113)	
	<u>Beta-2 microglobulins</u>		<u>Beta-2 microglobulins</u>		<u>Beta-2 microglobulins</u>	
	<u>$\mu\text{g/l}$ density corrected</u>	<u>$\mu\text{g/g}$ creatinine corrected</u>	<u>$\mu\text{g/l}$ density corrected</u>	<u>$\mu\text{g/g}$ creatinine corrected</u>	<u>$\mu\text{g/l}$ density corrected</u>	<u>$\mu\text{g/g}$ creatinine corrected</u>
Mean	122.8	82.0	127.4	88.1	156.1	106.8
Standard deviation	119.5	103.7	117.5	84.9	187.7	141.6
Median	97	63	93.5	67	116	72
Range	3 - 1135	2 - 1760	8 - 740	6 - 491	6 - 1270	3 - 1061

Table 3 - 28

Correlations between urinary beta-2 microglobulin levels
($\mu\text{g/g}$ creatinine) and age, in copper smelter employees
and miners

	<u>Age</u>	
	<u>Copper smelter employees</u>	<u>Miners</u>
Urinary beta-2 microglobulins (log transformed)	$r = 0.119$ $p = 0.002$	$r = 0.109$ $p = 0.12 \text{ n.s.}$

may indicate an effect of the smelter environment. Nevertheless, in the absence of any significant correlations between urinary excretion of β -2 microglobulin and Cd-U, Cd-B, the causal relationship with increased cadmium absorption is not certain.

The results of the analysis of renal function (BUN, serum creatinine, and urinary β -2 microglobulin) in this group of copper smelter employees indicated only indirectly that kidney function could be impaired by long-term exposure in the smelter. The relevant findings are limited to:

- a significant correlation between serum creatinine and age (a relationship not present in populations not exposed to nephrotoxic agents), serum creatinine and duration of smelter employment and between serum creatinine and Cd-U, and
- a significant correlation between urinary β -2 microglobulin levels and age, present in copper smelter workers, but not found in miners.

The renal effects of cadmium and lead in this population of copper smelter workers were clinically less evident than those reported for other cadmium-exposed occupational groups,³ or those found by us in lead-exposed groups.² The results of the present study indicate that effects on renal function at the low levels of cadmium and lead absorption that were observed in this smelter population are very limited.

Calcium and phosphorus metabolism

An effect of increased cadmium body burden on calcium and phosphorus metabolism has been reported in occupationally-exposed workers and also in environmentally-exposed populations.^{10 11} Although this problem has been extensively investigated, especially in Japan, where Itai-Itai disease has occurred in endemic proportions in geographic areas with significant environmental cadmium contamination, a generally accepted mechanism for these biological effects of cadmium has not yet been identified.

In the copper smelter population studied, calcium, phosphorous, and alkaline phosphatase blood levels were measured (Tables 3-29, 3-30) and correlations with blood cadmium and urinary cadmium were investigated. Comparisons with findings in the 142 miners subgroup (who had never been employed in the copper smelter) were also made.

The following observations were of interest:

- Significant positive correlations between serum calcium and blood cadmium in copper smelter workers; no such correlation was found in miners (Table 3-31).
- Significant positive correlations between serum phosphorus and blood cadmium in copper smelter workers (Table 3-32).
- Significant negative correlations between serum calcium and urinary cadmium (Table 3-33) in copper smelter employees (not in miners).
- No significant correlation between serum phosphorus and urinary cadmium (Table 3-34).
- Alkaline phosphatase levels were found to be positively and highly significantly correlated with Cd-B and Cd-U in copper smelter workers (Tables 3-35, 3-36).

Tentative explanation for these observations could be found in early effects of cadmium absorption, as reflected in increased Cd-B, resulting in higher serum calcium and alkaline phosphatase (possibly mobilization from bone); an increase in urinary cadmium excretion, indicating an increase in cadmium body burden, could then result in an elevated urinary excretion of calcium and thus lower serum calcium levels. More complete studies of calcium metabolism in cadmium-exposed individuals, including measurements of urinary cadmium excretion, are necessary to further clarify these relationships.

Table 3 - 29

Distribution of serum calcium levels in
copper smelter employees and miners

<u>Calcium mg/dl</u>	<u>Copper smelter employees</u>				<u>Miners</u>	
	<u>Active</u>		<u>Retired</u>			
	N = 676		N = 94		N = 142	
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>
< 9	8	1.2	1	1.1	0	-
9 - 10	361	53.6	50	53.2	90	63.4
10.1 - 11	286	42.4	39	41.5	50	35.2
> 11	19	2.8	4	4.3	2	1.4

Table 3 - 30

Distribution of serum phosphorous levels
in copper smelter employees and miners

	<u>Copper smelter employees</u>				<u>Miners</u>	
	<u>Active</u>		<u>Retired</u>			
	N = 578		N = 78		N = 128	
<u>Phosphorus in mg/dl</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>
< 2.5	55	9.5	3	3.9	6	4.7
2,5 - 4.5	510	88.2	73	93.6	117	91.4
> 4.5	13	2.3	2	2.6	5	3.9

Table 3 - 31

Correlations between blood calcium and cadmium
in copper smelter employees and miners

	<u>Copper smelter employees</u>				<u>Miners</u>	
	Total (active and retired)		Active employees only		CdB	log CdB
	<u>CdB</u>	<u>log CdB</u>	<u>CdB</u>	<u>log CdB</u>		
Calcium mg/dl	r = 0.111 p = 0.001		r = 0.101 p = 0.004		r = 0.083 p = 0.163 n.s.	
log Calcium		r = 0.105 p = 0.002		r = 0.099 p = 0.005		r = 0.086 p = 0.154 n.s.

Table 3-32

Correlations between blood phosphorus and
cadmium in copper smelter employees
and miners

	<u>Copper smelter employees</u>				<u>Miners</u>	
	Total (active and retired)		Active employees only		CdB	log CdB
	CdB	log CdB	CdB	log CdB		
Phosphorus mg/dl	r = 0.123 p = 0.0008		r = 0.137 p = 0.0005		r = 0.072 p = 0.21 n.s.	
log Phosphorus		r = 0.147 p = 0.00008		r = 0.159 p = 0.00006		r = 0.158 p = 0.038

Table 3 - 33

Correlations between blood calcium and urinary cadmium
in copper smelter employees and miners

	<u>Copper smelter employees</u>		<u>Miners</u>	
	Total (active and retired)	Active employees only	CdU $\mu\text{g/g creat}$	log CdU
Calcium mg/dl	$r = -0.046$ $p = 0.116$ n.s.	$r = -0.080$ $p = 0.025$	CdU $\mu\text{g/g creat}$	log CdU
			$r = -0.0005$ $p = 0.497$ n.s.	
log Calcium		$r = -0.081$ $p = 0.017$	$r = -0.107$ $p = 0.004$	$r = 0.066$ $p = 0.23$

Table 3 - 34

Correlations between blood phosphorus and
urinary cadmium in copper smelter
employees and miners

	<u>Copper smelter employees</u>		<u>Miners</u>
	Total (active and retired)	Active employees only	
	<u>CdU $\mu\text{g/g creat}$ log CdU</u>	<u>CdU $\mu\text{g/g creat}$ log CdU</u>	<u>CdU $\mu\text{g/g creat}$ log CdU</u>
Phosphorus mg/dl	r = -0.005 p = 0.449 n.s.	r = -0.035 p = 0.215 n.s.	r = 0.098 p = 0.151 n.s.
log Phosphorus	r = -0.031 p = 0.229 n.s.	r = -0.054 p = 0.112 n.s.	r = 0.164 p = 0.041

Table 3 - 35

Correlations between alkaline phosphatase and
blood cadmium in copper smelter employees
and miners

	<u>Copper smelter employees</u>				<u>Miners</u>	
	Total (active and retired)		Active employees only		CdB	log CdB
<u>Alkaline phosphatase U/l</u>	<u>CdB</u>	<u>log CdB</u>	<u>CdB</u>	<u>log CdB</u>	<u>CdB</u>	<u>log CdB</u>
Alkaline Phosphatase	$r = 0.120$ $p = 0.0004$		$r = 0.127$ $p = 0.0005$		$r = 0.156$ $p = 0.033$	
log Alkaline Phosphatase		$r = 0.190$ $p < 0.000001$		$r = 0.196$ $p < 0.000001$		$r = 0.134$ $p = 0.056$

Table 3 - 36

Correlations between alkaline phosphatase and
urinary cadmium in copper smelter employees
and miners

	<u>Copper smelter employees</u>				<u>Miners</u>	
	Total (active and retired)		Active employees only			
<u>Alkaline phosphatase U/l</u>	<u>CdU µg/g creat</u>	<u>log CdU</u>	<u>CdU µg/g creat</u>	<u>log CdU</u>	<u>CdU µg/g creat</u>	<u>log CdU</u>
Alkaline phosphatase	r = 0.210 p < 0.000001	/	r = 0.232 p < 0.000001		r = 0.182 p = 0.021	
log Alkaline phosphatase		r = 0.226 p < 0.000001		r = 0.244 p < 0.000001		r = 0.139 p = 0.061

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Chapter IV

Neurobehavioral evaluation of copper smelter workers

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One purpose of this study was to determine whether central nervous system effects of the type found in other lead-exposed groups occur in copper smelter workers exposed to lead present as an impurity in the copper concentrate. Lead is a known neurotoxic agent and neurobehavioral effects have been demonstrated at relatively low levels of absorption (Hänninen, et al., 1978; Valciukas et al., 1978). We had reported earlier that secondary lead smelter workers had significantly lower performance test scores than non-exposed controls. Lead absorption as reflected by blood lead (Pb-B) and zinc protoporphyrin (ZPP) levels was significantly correlated with decrements in performance test results (Valciukas, et al., 1980).

We studied the correlation between indicators of lead absorption and performance tests in 228 copper smelter workers employed at Noranda. Table 4-1 shows the number of subjects in each job category. Performance tests were administered in French or English by specially trained bilingual personnel.

The following performance tests were used: the Block Design, Digit Symbol, and Embedded Figures Tests. For the Block Design Test, the subject is presented with a set of cubes whose faces are red, white, and half red and half white. The subject is asked to arrange the cubes within a time limit in a way that duplicates a pattern shown to him (Wechsler, 1955). For the Digit Symbol Test, the subject is given a list in which symbols are associated with the digits 1 to 9 and is asked to enter the appropriate symbols in blank spaces next to a list of random digits (Wechsler, 1955). For the Embedded Figures Test, the subject is shown four sets of ten superimposed outline drawings of common objects and is required to identify as many objects as possible (Valciukas and Singer, 1982). Illustrations of the performance tests and a more detailed description of their uses can be found elsewhere (Valciukas et al., 1978; Valciukas and Lilis, 1980).

Since most of the subjects were French-speaking, we investigated whether the overall age trends were different from English-speaking controls (Fig. 4-1). We found that except for the relatively lower correlation coefficient for the Digit Symbol Test, age trends were quite similar.

Table 4 - 1Job Categories

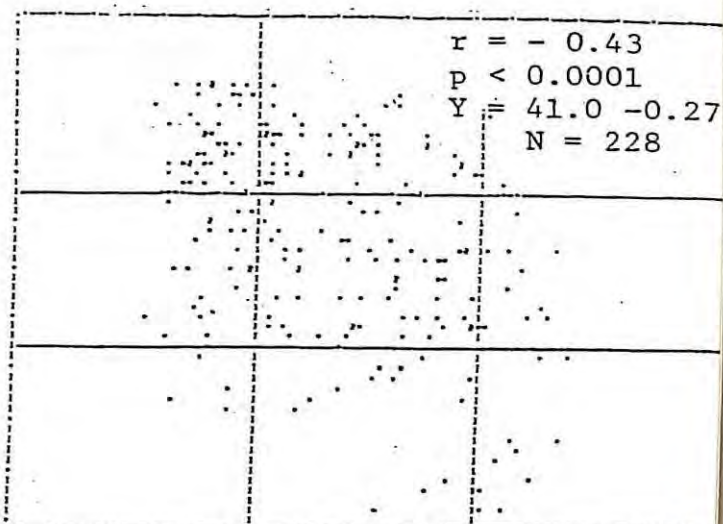
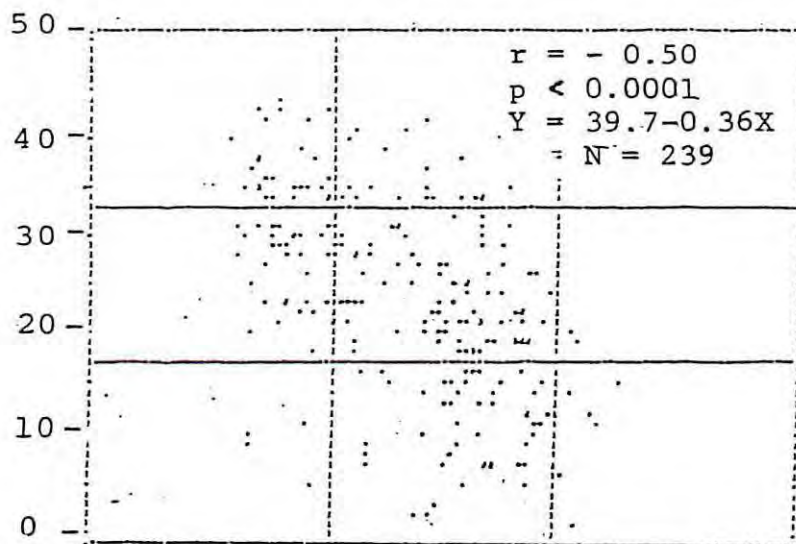
	<u>Number</u>
Concentrator	6
Concentrator unloading shed	5
Roasting or mixing	3
Furnace operator	23
Dust collector	5
Reactor feeder	21
Slag dumper	6
Convertor	22
Convertor craneman	5
Casting and shipping	6
Machine shop	3
Electrical shop	4
Scrap building	6
Power house and boiler	4
Oxygen plant	3
Slag department	1
Sample mill	6
Railroad construction yard	5
Power house and boilers	6
Painter	1
Carpenter	2
Rigger	6
Heavy equipment maintenance	11
Bricklayers	3
Pipefitters and plumbers	6
Laborers (inside)	2
Laborers (outside)	2
Welder	1
Other jobs	54

CONTROLS

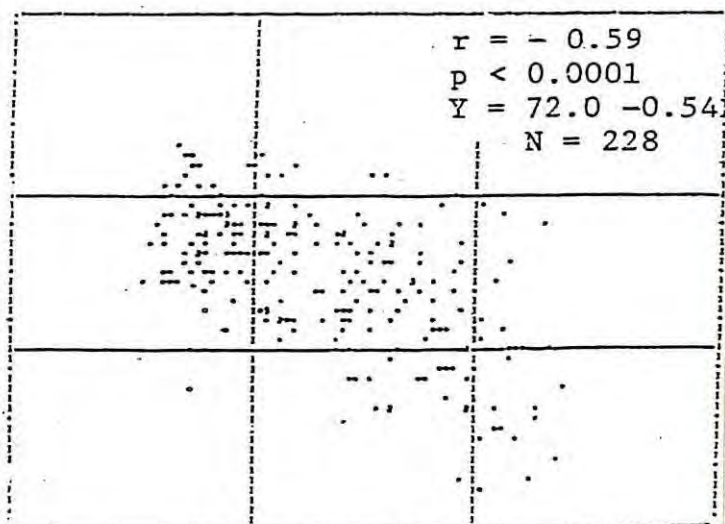
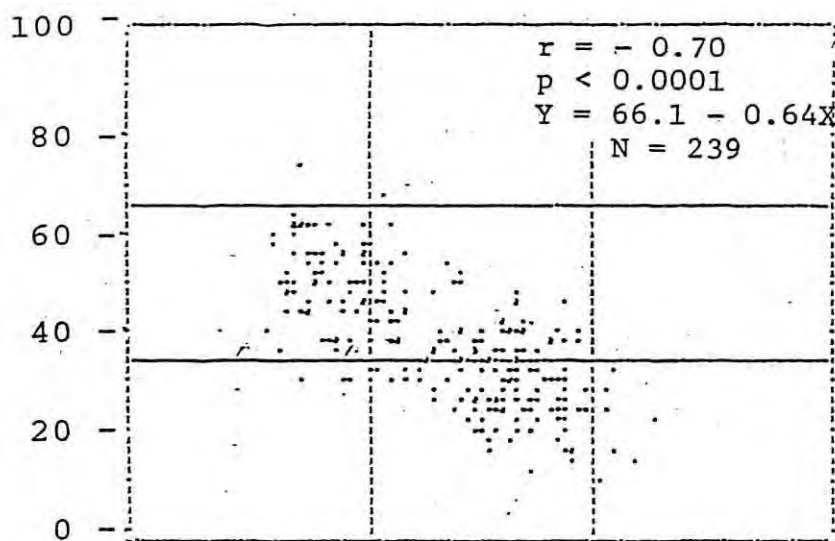
106

COPPER SMELTER
WORKERS

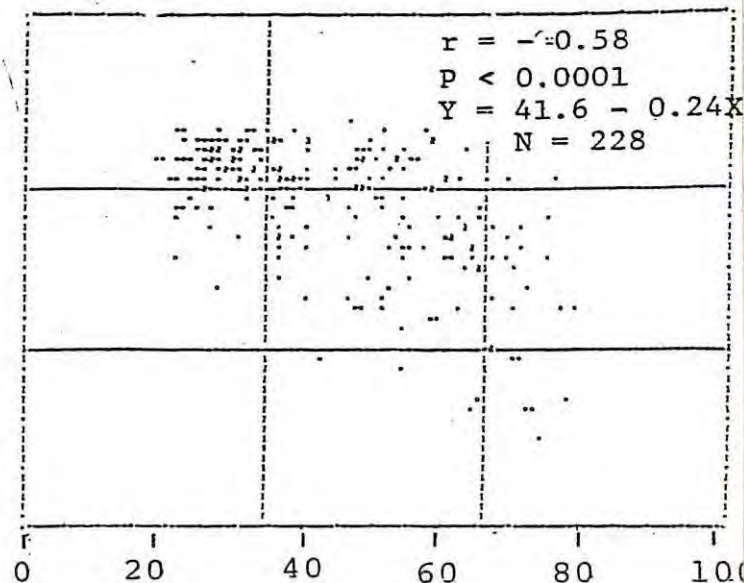
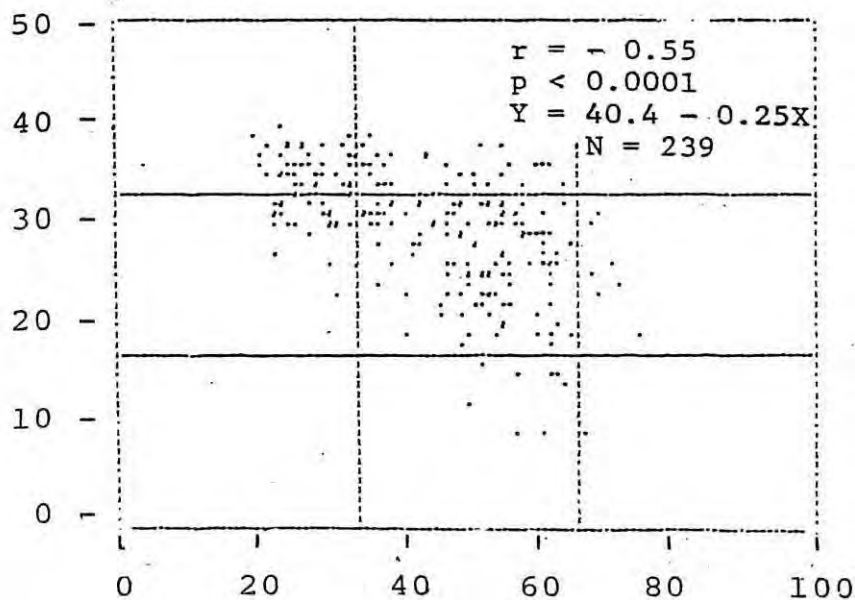
BD



DS



EF



AGE

AGE

Fig. 4-2 shows distribution patterns for Pb-B and ZPP levels in the group studied. Both indicators of lead absorption were in a relatively low range. Further discussion of distribution patterns for this and other metals is found in Chapter II.

Fig. 4-3 shows the scattergrams of age-corrected performance test scores and ZPP in the study and control groups. Age-correction procedures are explained in a recent publication (Valciukas et al., 1981). Briefly, each performance test score (BD, DS and EF) was transformed to Z scores as follows. The expected value of each test score (BD', DS' and EF') was calculated on the basis of linear age trends observed in the control group. The ratios S.BD, S.DS and S.EF were computed as $S.BD = BD/BD'$, $S.DS = DS/DS'$, and $S.EF = EF/EF'$. If BD is identical to BD', S.BD is equal to 1. Z.BD is defined as $Z.BD = (BD/BD' - 1)/SD$.

Although the scattergrams are somewhat different in the magnitude of the spread, no significant correlations between ZPP and age-standardized scores were observed for any of the three tests. When the three standardized scores were combined in an index (Z.CNS) (Valciukas et al., 1981) no significant correlations were observed between Z.CNS and Pb-B or ZPP levels (Fig. 4-4).

Conclusion

Lead exposure in this group of copper smelter workers was low and at levels not known to be associated with decrement in brain function as assessed by this limited battery of neurobehavioral tests. In a recent publication (Valciukas and Lilis, in press), we compared four occupational groups with different levels of lead absorption. The copper smelter group studied here was characterized by the lowest level of lead absorption and did not exhibit correlations between standardized test scores and biological indicators of lead exposure. Scattergrams of performance test scores were similar to those expected in a normal, non-lead-exposed population.

Copper Smelter Workers (N=169)

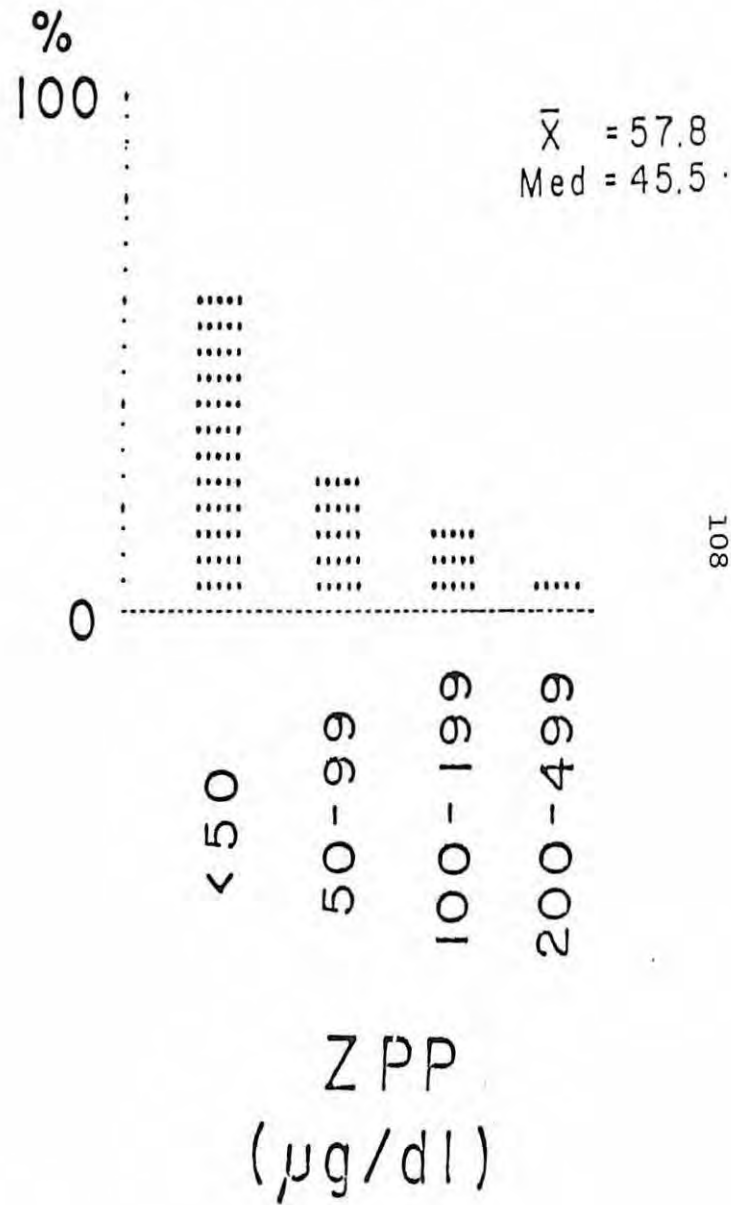
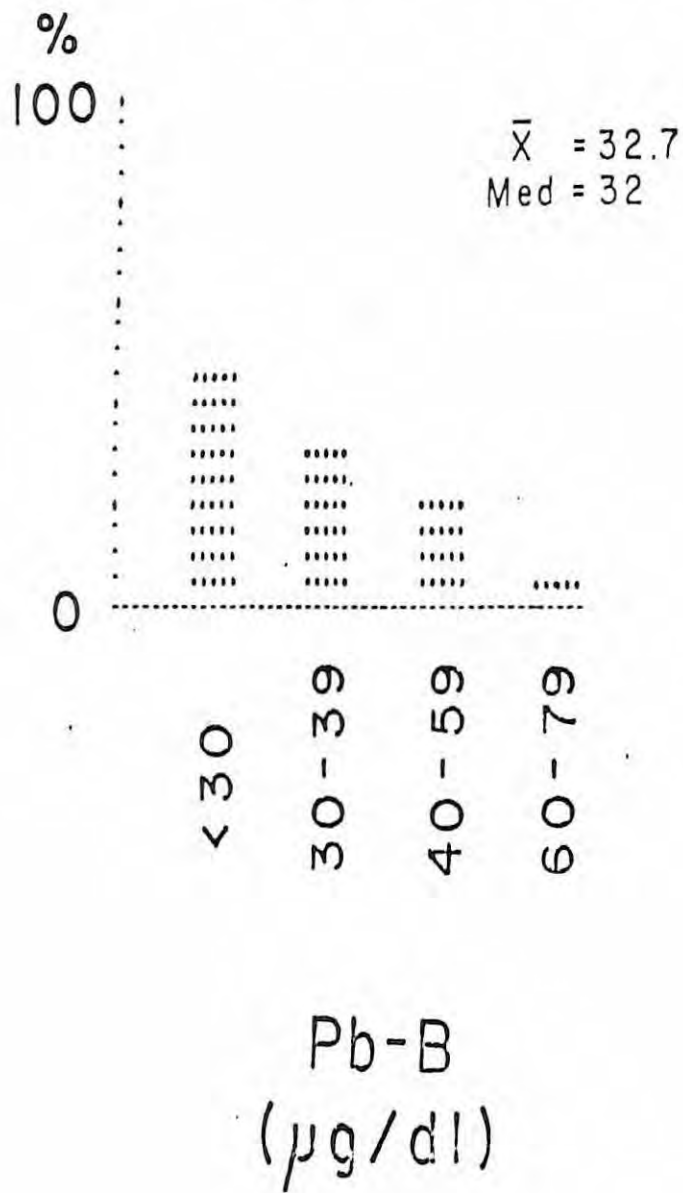


Figure 4-2

Z·BD

Z·DS

Z·EF

Copper Smelter Workers (N=169)

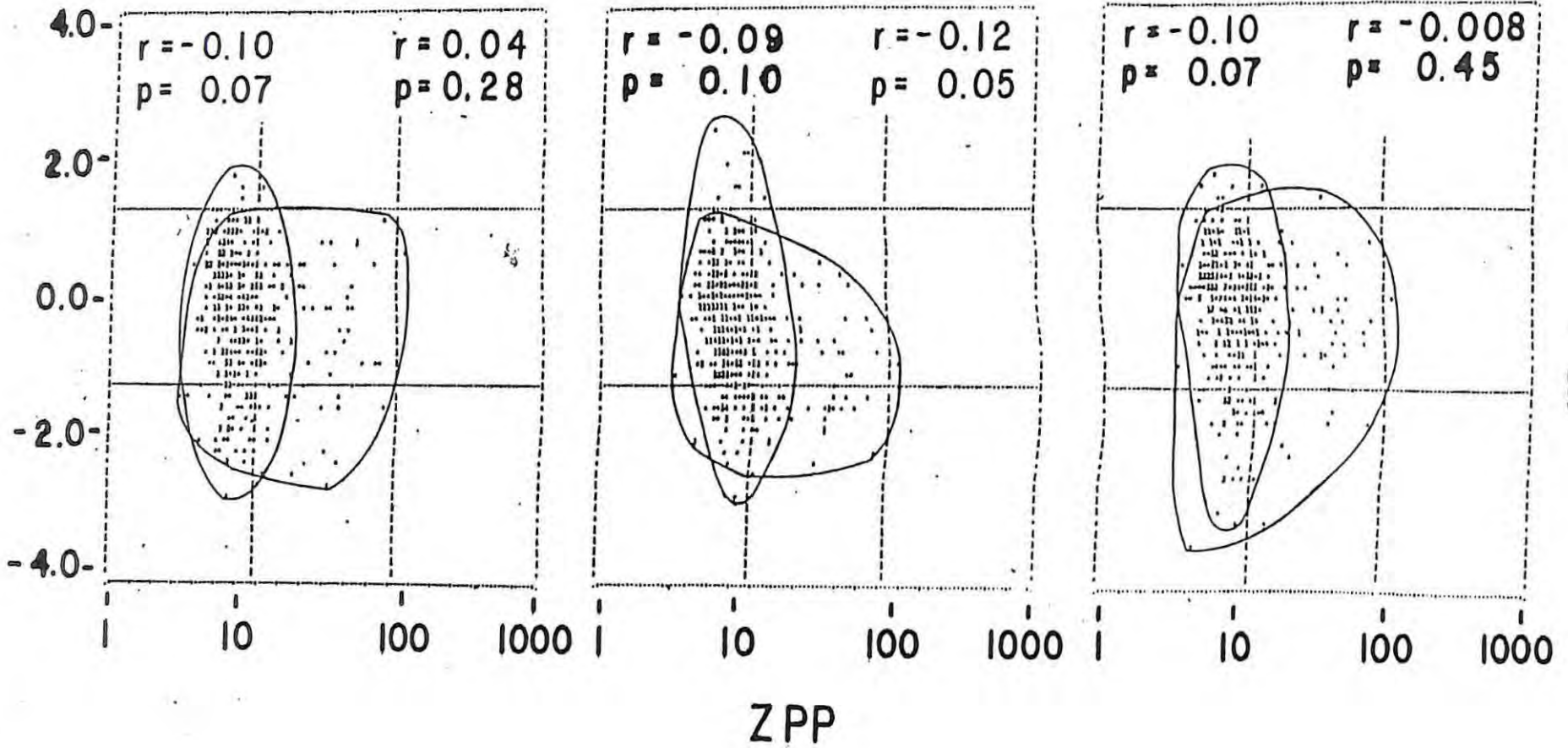


Figure 4-3

Z·CNS

Copper Smelter Workers (N=169)

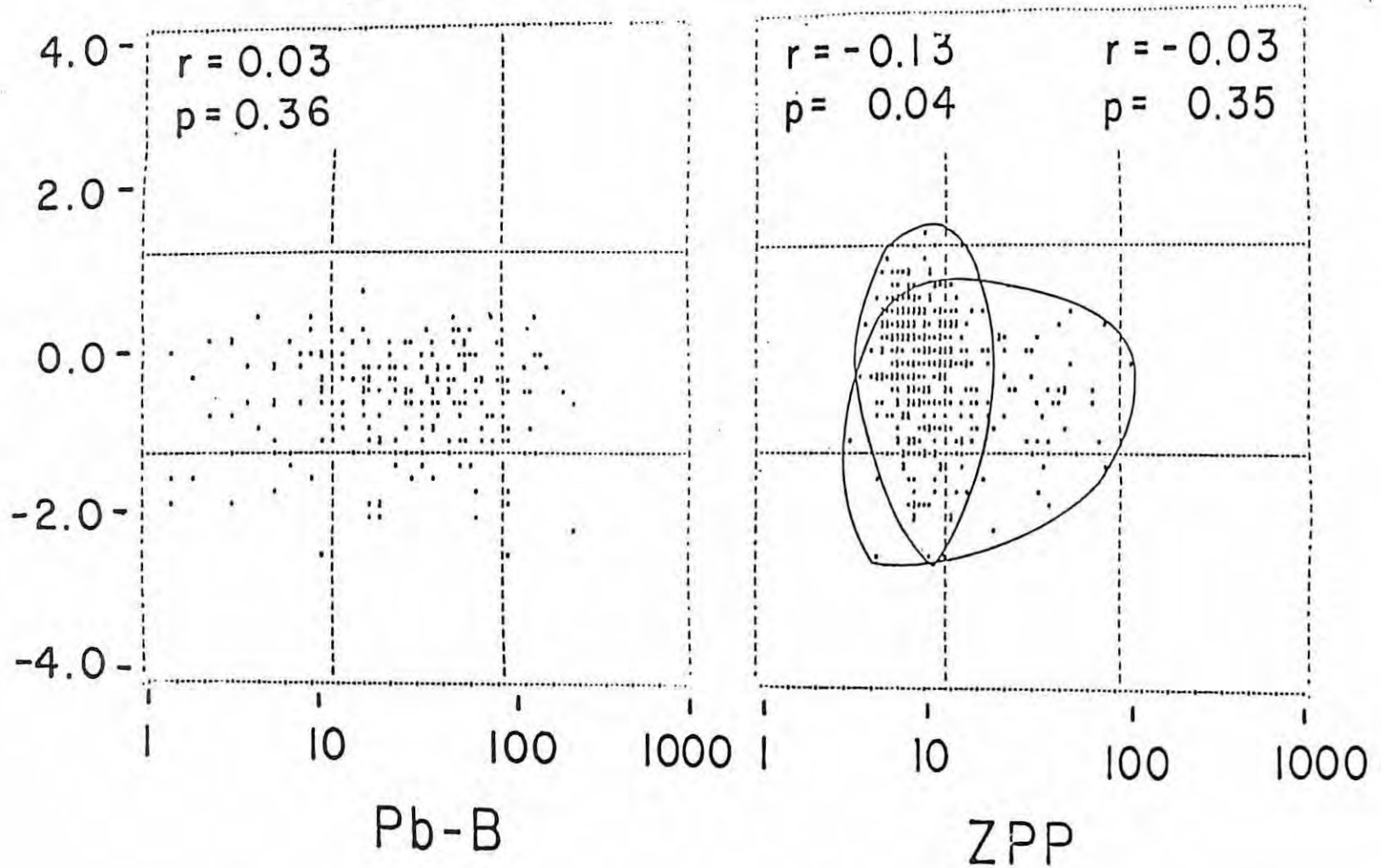


Figure 4-4

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CHAPTER V

Oculomotor studies in lead and arsenic-exposed
copper smelter workers

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Introduction

A purpose of this investigation was to study the effects on the central nervous system (CNS) of chronic lead and arsenic exposure in copper smelter workers using saccadic eye movements as an index of dysfunction. Saccadic eye movements are rapid, conjugate movements of the eyes from one stationary point in the visual field to the next. Precisely how the central nervous system generates saccades is still speculative, although many of the neural control centers have been identified. These include the cerebellum, the vestibular system, parts of the reticular formation and several nuclei in the brainstem.¹

Very few attempts to study neurotoxicity affecting the oculomotor system have been reported. In a recent study on the effects of inorganic lead on the oculomotor system in a group of secondary lead smelter workers and non-lead exposed controls, no significant differences between lead workers and controls were found for measures of optokinetic nystagmus or smooth pursuit movements. Mean accuracy of saccadic eye movements was found to be significantly different between the two groups. However, saccade accuracy was not significantly correlated with blood lead levels (Pb-B) or with delta-aminolevulinic acid dehydratase (ALA-D). Significant differences in saccade delay time were found between controls and a subgroup of lead workers with blood lead levels greater than 60 µg/dl. No significant correlations were reported between eye movement measurements and whole blood or hair arsenic levels.² Results of a follow-up study conducted on these same workers 12 to 18 months later were consistent with those of the initial study with the exception that a negative correlation between blood lead levels and maximum saccade velocity was observed.^{3 4}

Recently, we conducted an investigation to determine the effects of chronic, low-level exposure to inorganic lead on quantitative measures of saccadic eye movements in automobile production workers. The results indicated that workers exposed to inorganic lead showed statistically significant differences when compared to controls, on all of the measures of eye movements studied (total number of eye movements, saccades-to-target, overshoots and velocity). In addition, both total number of eye movements

and the number of saccadic eye movements to fixate the targets were significantly correlated with Pb-B levels of both blood lead (Pb-B) and zinc protoporphyrin (ZPP). Velocity of saccadic eye movements was not correlated with Pb-B levels, but a highly significant correlation between velocity and ZPP levels was observed.⁵

Current study

The main purpose of the current investigation was to examine the effects of chronic exposure to inorganic lead and arsenic on saccadic eye movements in individuals occupationally exposed to these agents in a large copper smelter. Specifically, attempts were made: 1) to quantify measures of saccadic dysmetria; 2) to compare quantitative measures of saccadic eye movements in individuals exposed to inorganic lead and arsenic with a similar group not so exposed; and 3) to correlate the quantitative measures obtained with biological indicators of lead and arsenic, particularly ZPP, Pb-B levels and urinary arsenic (As-U).

Methods

Apparatus

The instrumentation used was designed to elicit, record and measure saccadic eye movements under medical field survey conditions. The apparatus consists of a programmable visual display unit and a recording system. The programmable visual display unit consists of five point sources of light appearing in the horizontal plane. The light sources are mounted so that one of the lights is directly at the center of visual fixation and the other lights subtend visual angles 7.5 and 15 degrees to the left and right of center when viewed at a distance of 2.68 meters. Therefore, saccadic eye movements to eight stimulus combinations are possible: 7.5, 15.0, 22.5 and 30 degrees from left to right and from right to left. The lights are switched on and off by means of a silent programmable switch according to a program which repeats itself automatically.

An infrared system is used to record saccadic eye movements. Eye movements are recorded mono-ocularly from the right eye. The system consists of a modulated gallium arsenide infrared light source flanked by a pair of silicon phototransistors mounted on a spectacle frame. This is connected to an amplifier-demodulator unit (Gulf & Western, Model 200). The amplifier-demodulator converts the current produced by the phototransistors into an output voltage proportional to the angular displacement of the eye. The output from the amplifier-demodulator is displayed on an inkwriting physiograph (Narco, Model DMP-4B) equipped with a DC-AC coupler (Narco, Type 7301). The DC-AC coupler translates the output voltage from the amplifier-demodulator into a pen deflection which is proportional to that voltage. The amplitude of saccadic eye movements can, therefore, be accurately recorded.

Subjects

This investigation was conducted during a cross sectional medical examination of 920 copper smelter workers: the 680 active employees, 96 retirees and 144 miners (see Chapter I for full description). A subsample of these workers underwent testing of oculomotor performance. Since the testing procedure requires 20-30 minutes, it was possible to examine oculomotor behavior in 94 individuals. A separate group of 52 workers with no history of exposure to neurotoxic agents comprised the control group. It included blue collar workers from several sources; insulators (N = 8), brakeworkers (N = 7), and hospital employees (N = 16). In addition, 21 control subjects were chosen from a group of men either awaiting treatment at one of the various clinics at Mount Sinai Hospital or who had come to the clinic to accompany a friend or relative. No subjects reporting eye, nose, throat or nervous system conditions were tested.

The occupations of the men in the latter group were varied. An occupational history was taken to eliminate control subjects exposed to neurotoxic agents. A more detailed description of the control group, including job descriptions, is to be found in Glickman, 1982.⁶ Workers in the study and control groups were group-matched for age.

Table 5-1 shows the age distribution of copper smelter workers and controls. Workers in the study group ranged in age from 19-67 years; the mean age was 38.6. Workers in the control group ranged in age from 20-64 years with a mean age of 37.9. Results of a t-test showed no significant age difference between the two groups ($t=0.30$, n.s.; Table 5-5).

Table 5-2 shows the distribution of Pb-B and ZPP levels in the study group. Blood lead levels ranged from 6.9 to 62.3 $\mu\text{g}/\text{dl}$. Most of these workers (81.9%) had Pb-B levels less than 40 $\mu\text{g}/\text{dl}$; 17% had levels between 40-60 $\mu\text{g}/\text{dl}$; and only one worker (1.1%) had a blood lead level greater than 60 $\mu\text{g}/\text{dl}$. ZPP levels ranged from 21-181 $\mu\text{g}/\text{dl}$. Sixty workers in the study group (74.5%) had ZPP levels less than 50 $\mu\text{g}/\text{dl}$; 23.4% had levels ranging from 50-100; and 11.8% had ZPP levels in excess of 100 $\mu\text{g}/\text{dl}$.

Table 5-3 presents specific-gravity corrected urinary arsenic levels for the group of copper smelter workers. Urinary arsenic levels ranged from 3-120 $\mu\text{g}/\text{l}$. Most examinees (86.1%) had As-U levels less than 49 $\mu\text{g}/\text{l}$; 9.3% had levels between 50-99 $\mu\text{g}/\text{l}$; and 4.6% had levels greater than 99 $\mu\text{g}/\text{l}$.

The duration of employment of workers in the study group is presented in Table 5-4. Many of the workers (43%) were employed at the copper smelter for more than ten years; 35.5% were employed for five years or less.

Results

The characteristics of saccadic eye movements investigated in this study were total number of eye movements executed during the test session and number of saccadic eye movements to fixate the target (saccades-to-target). These measures have been shown to be reliable indicators of saccadic dysmetria.⁵ Results of between-group and within-group comparisons are presented below.

Table 5 - 1Age distribution of copper
smelter workers and controls

<u>Age</u>	<u>Copper smelter workers (N=94)</u>		<u>Controls (N=52)</u>	
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>
20 - 29	29	(30.9)	23	(44.2)
30 - 39	26	(27.6)	8	(15.4)
40 - 49	16	(17.0)	10	(19.2)
50 and older	23	(24.5)	11	(21.2)

Table 5 - 2Blood lead and ZPP levels in
copper smelter workers

N = 94

<u>Blood lead level ($\mu\text{g}/\text{dl}$)</u>	<u>N</u>	<u>%</u>
< 40	77	81.9
40 - 60	16	17.0
> 60	1	1.1

N = 93

<u>ZPP level ($\mu\text{g}/\text{dl}$)</u>	<u>N</u>	<u>%</u>
< 50	60	64.5
50 - 100	22	23.4
> 100	11	11.8

Table 5 - 3Urinary arsenic (density corrected)
in copper smelter workers

N = 86

<u>Urinary arsenic ($\mu\text{g}/\text{l}$)</u>	<u>N</u>	<u>%</u>
< 20	36	41.9
20 - 49	38	44.2
50 - 99	8	9.3
\geq 100	4	4.6

Table 5 - 4Duration of employment in copper smelter workers(N = 93)

<u>Duration (years)</u>	<u>No.</u>	<u>%</u>
<u>≤ 1</u>	10	10.8
1.1 - 3	13	13.9
3.1 - 5	10	10.8
5.1 - 10	20	21.5
10.1 - 20	23	24.7
> 20	17	18.3

1. Between-Group Comparisons

Table 5-5 presents the results of a t test analysis comparing oculomotor function measures in copper smelter workers and controls. The t-tests showed significant differences between study and control workers in mean values for both total number of eye movements ($t = 7.12$, $p < 0.0001$) and saccades-to-target ($t = 7.69$, $p < 0.0001$).

2. Within-Group Comparisons

The relationship between oculomotor function measures and biological indicators of lead and arsenic exposure in the copper smelter workers was explored using correlational analysis. Table 5-6 shows that no significant correlation was observed between total number of eye movements and biological indicators of exposure (Pb-B, ZPP and As-U). Similarly, no significant correlation between saccades-to-target and biological indicators of lead and arsenic exposure was observed.

Discussion

Statistically significant differences between copper smelter workers and controls were found for both total number of eye movements and saccades-to-target. These findings suggest that exposure to neurotoxic agents in the copper smelter is associated with measureable adverse effects on the oculomotor system.

The fact that within the group of copper smelter workers no significant correlation between measures of eye movements and biological indicators of lead and/or arsenic exposure were observed can be explained by careful examination of the biological indicators of exposure characteristics for this group. First, as described above, Pb-B, ZPP and As-U levels were relatively low in many of the workers examined. Further, the range of the values for the three biological indicators of lead and arsenic exposure was relatively narrow. This also is the most likely explanation for the differences in the oculomotor function test results in copper smelter workers and automobile production workers.

Table 5 - 5

Results of t-test analysis comparing oculomotor function
measures in copper smelter workers and controls

	<u>Study group</u> (N = 94)	<u>Control group</u> (N = 52)
	Mean ± SD	Mean ± SD
Total number of eye movements	180.9 ± 38.3	138.2 ± 26.7
		t = 7.12 p = 0.0001
Saccades-to- target	161.8 ± 27.9	129.6 ± 15.3
		t = 7.69 p = 0.0001
<hr/>		
Age	38.5 ± 12.7	37.9 ± 13.0
		t = 0.30 n.s.

Table 5 - 6

Relationship between oculomotor function measures and biological indicators of lead and arsenic exposure in copper smelter workers

Measures of eye movements

Biological indicators of exposure	Total number of eye movements	Saccades-to-target
Blood lead	r = 0.02 n.s.	r = -0.05 n.s.
ZPP	r = 0.10 n.s.	r = 0.11 n.s.
Urinary arsenic	r = 0.13 n.s.	r = -0.01 n.s.

As described above, we found that like the copper smelter workers, automobile production workers exposed to inorganic lead showed statistically significant differences in total number of eye movements and saccades-to-target compared to controls. In addition, total number of eye movements and saccades-to-target were significantly correlated with both blood lead and ZPP levels in the groups of automobile production workers (Table 5-7).

Table 5-8 presents Pb-B and ZPP levels in automobile production workers. It can be seen that workers with a wide range of blood lead and ZPP levels comprised this group. Approximately 34% of these workers had blood lead levels above 60 $\mu\text{g}/\text{dl}$. Relatively few automobile production workers (15.4%) had blood lead levels less than 40 $\mu\text{g}/\text{dl}$. Blood lead levels ranged from 18-94 $\mu\text{g}/\text{dl}$ compared to 6.9-62.3 $\mu\text{g}/\text{dl}$ in the group of copper smelter workers. Table 5-8 also shows that almost half of the automobile production workers (48%) had ZPP levels higher than 100. Only 13.5% had ZPP levels less than 50, while 19.2% had ZPP levels in excess of 200. ZPP levels ranged from 34 to 540 $\mu\text{g}/\text{dl}$ compared to 21-181 $\mu\text{g}/\text{dl}$ in copper smelter workers. It is clear that the mean of the distribution of Pb-B and ZPP levels in copper smelter workers, described above and presented in Table 5-2, was shifted towards lower levels - lower than those in the automobile production workers. Despite these relatively low Pb-B and ZPP values, copper smelter workers were found to have significantly higher total number of eye movements and saccades-to-target than controls.

The results of this study suggest that the oculomotor system is vulnerable to the effects of neurotoxic agents found in the copper smelter. Chronic, low-level exposure to these agents has been shown to be associated with disturbances in the ability to move the eyes smoothly from one stationary point in the visual field to the next (saccade dysmetria).

Table 5 - 7

Relationship between oculomotor function measures and
biological indicators of lead exposure in automobile
production workers

Measures of eye movements

	Total number of eye movements	Saccades-to- target
Biological indicators of lead exposure		
Blood lead	r = 0.27 p < 0.05	r = 0.37 p < 0.005
ZPP	r = 0.37 p < 0.005	r = 0.40 p < 0.005

Table 5 - 8Blood lead and ZPP levels in automobile
production workers (N = 52)

<u>Blood lead levels ($\mu\text{g}/\text{dl}$)</u>	<u>N</u>	<u>%</u>
< 40	8	15.4
40 - 60	26	50.0
> 60	18	34.7
<u>ZPP levels ($\mu\text{g}/\text{dl}$)</u>		
< 50	7	13.5
50 - 100	20	38.5
> 100	25	48.0

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CHAPTER VI

Nerve Conduction Velocity Assessment
of
Copper Smelter Workers

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Potential effects of arsenic and lead on the peripheral nervous system.

Arsenic and lead are contained in copper ore and in the copper concentrate - the raw material of the smelting process - and can be found in airborne dust when the concentrates are moved or stored. When heat is applied during pyrometallurgic smelting, arsenic is released as arsenic trioxide fumes (Gomez et al., 1979).

Chronic exposure to arsenic can affect the skin, mucous membranes, hemato-poietic system, liver, heart, and is suspected to be carcinogenic. Acute exposure can produce neurological symptoms 10 days to 3 weeks following exposure (Heyman et al., 1956; Chhuttani et al., 1967; LeQuesne and McLeod, 1977). Sensory symptoms of numbness and paresthesia, particularly of the distal extremities, is followed by weakness. The lower limbs are often affected before the upper limbs. Recovery is gradual and can be complete in mild cases. The pattern of peripheral nervous system (PNS) effects following chronic exposure seems similar to that found following a single massive exposure, but at a slower pace.

A number of researchers have used nerve conduction velocity measurement (NCV) for objective and quantitative assessment of arsenic effects on the PNS. Goldstein et al. (1975) reported reduction of motor NCV and marked disruption of the sensory action potential in nine patients accidentally exposed to arsenic in unrelated incidents. Hindmarsh et al. (1977) reported a study of 92 people using water from wells with high arsenic levels and found that neural dysfunction was associated with levels of water contamination. Sensory effects were more marked than motor effects. Arsenic in hair and NCV findings were not strongly correlated. LeQuesne and McLeod (1977) studied four patients who developed peripheral neuropathy following a single dose of arsenic. The same pattern of sensory disruption more marked than motor was found. The four patients improved slowly, but three still showed symptoms and/or signs after six years. Histopathologic examination showed axonal degeneration with no segmental demyelination, (as also reported by Heyman et al. (1956), Ohta (1970), and Goldstein et al. (1975)).

Lead, as noted previously in this report, is also found in copper ore concentrate; its neurotoxic properties have been widely studied. A review of studies of lead effects using NCV on the PNS is available (Singer and Valciukas, 1982).

An early study of NCV changes associated with lead exposure is that by Sessa et al. (1965). They found a reduction in motor velocity of the ulnar and radial nerves in 20 lead-poisoned patients without clinical signs of neurological impairment.

Seppäläinen et al. (1979) studied 78 workers, occupationally exposed to lead, whose Pb-B levels had been monitored regularly. Motor NCV was decreased in the median, ulnar, and posterior tibial nerves, while sensory NCV was decreased in the median and ulnar nerves. NCV of the median motor and sensory, ulnar slow fibers, ulnar sensory, and posterior tibial were negatively correlated with maximal Pb-B levels, time weighted average Pb-B, and current Pb-B. Abnormal NCV values were found in 27% of the subgroup whose maximal Pb-B did not exceed 49 $\mu\text{g}/\text{dl}$.

Seppäläinen and Hernberg (1980) reported a prospective study of 100 lead workers. Median sensory and motor NCV were assessed, along with Pb-B and ZPP at three yearly intervals. Only 16 of the 100 subjects were still employed with the company at the end of two years. Subjects with higher ZPP levels (mean values of 69 $\mu\text{g}/\text{dl}$) had slower motor and distal sensory NCV of the median nerve at the end of two years employment.

In a recent study of the temporal pattern of lead effects on the PNS among automobile assembly workers (Singer, Valciukas and Lilis, 1981), sensory nerve effects preceded motor nerve effects.

Subjects

The subject of this study were 127 of the male copper smelter workers. Table 6-1 shows the demographic characteristics of the group. Mean age was 42.1 years and mean duration of employment was 12.0. Mean blood lead was relatively low for industrial exposure (32.8 $\mu\text{g}/\text{dl}$) and mean ZPP was 63.6 $\mu\text{g}/\text{dl}$. Mean urinary arsenic (As-U, density corrected) was 33.9 $\mu\text{g}/\text{l}$.

Table 6-1: Age, duration of exposure, blood lead, zinc protoporphyrin, and urine arsenic levels in copper smelter workers with nerve conduction velocity assessment

Lead and arsenic exposed (N=127)

	<u>Mean</u>	<u>Standard deviation</u>	<u>Range</u>
Age (years)	42.1	13.4	19.0 - 77.0
Duration of employment (years)	12.0	9.4	0.5 - 40.0
Blood lead (Pb-B) $\mu\text{g}/\text{dl}$	32.8	11.2	10.5 - 62.3
Zinc protoporphyrin (ZPP) $\mu\text{g}/\text{dl}$	63.6	38.5	26.0 - 198.0
Urine arsenic (density corrected) $\mu\text{g}/\text{l}$	33.9	26.3	3.0 - 120.0

Table 6-2 shows distribution of age, duration of employment, Pb-B, ZPP, and As-U values in copper smelter workers who were examined.

Methods

Nerve conduction velocities were assessed on the median motor (elbow to wrist), median sensory (wrist to index finger), peroneal (knee to ankle), and sural nerves (calf to heel). Antidromic stimulation of the sensory nerves was used. Stimulation was supramaximal. NCV procedures were standard and have been previously reported in detail (Singer et al., 1982).

All subjects were screened for diabetes, neurological disease, back injuries, and alcohol consumption of more than 28 alcoholic beverages per week. Only limbs that had suffered no significant trauma were tested. If the back had been injured, or if disk disease or "sciatica" were reported, the subjects' peroneal and sural nerves were not tested. If the neck had been severely injured, the arms were not tested.

The control group consisted of 31 male workers not employed at the smelter and without exposure to neurotoxic agents as determined by occupational history. The exclusion criteria for the exposed and control groups were identical. Measurement of latencies, temperature control, and calculation of velocities were performed at each examination site using identical procedures.

The t test analyses were performed on the NCV values to evaluate differences between the exposed and control groups. All values were then adjusted for age and temperature, and standardized so that a value of zero indicates the subjects' NCV value does not deviate from the value expected on the basis of age. The equations relating temperature and age with NCV were those reported in the literature. (See Singer, et al., 1982, for details).

The t tests were then performed on the standardized NCV values. These values were also used for the remaining correlational analyses, including correlation with years of employment, Pb-B, ZPP, and As-U (density corrected).

Table 6-2: Distribution of age, duration of employment, blood lead, zinc protoporphyrin, and urine arsenic values in copper smelter workers with nerve conduction velocity assessment.

<u>Age (years)</u>	<u>Lead and arsenic exposed</u>	
	<u>Number</u>	<u>Percent</u>
18-29	30	23.6
30-49	53	41.7
<u>>50</u>	44	34.6
<u>Duration of employment (years)</u>		
< 5	40	31.5
5- 9	25	19.7
10-19	37	29.1
<u>>20</u>	25	19.7
<u>Pb-B ($\mu\text{g}/\text{dl}$)</u>		
<40	94	74.0
40-59	31	24.4
60-79	2	1.6
<u>>80</u>	0	0.0
<u>ZPP ($\mu\text{g}/\text{dl}$)</u>		
< 50	65	51.0
50- 99	40	31.5
100-199	22	17.3
<u>>200</u>	0	0.0
<u>Arsenic density corrected ($\mu\text{g}/\text{l}$)</u>		
< 20	40	36.0
20- 49	48	43.7
50- 99	19	17.1
<u>>100</u>	4	3.6

Prevalence tables were constructed comparing slowing in sensory and motor nerves (defined as an NCV for which percentile rank for the normal population was 1 or less), in both the copper smelters and a comparison group with lead exposure only (automobile assembly workers, see Chapter III). Prevalence of slowing NCV within Pb-B levels was examined.

Results

The t test analyses of the mean NCV values, not standardized for age and temperature, are presented in Table 6-3. NCV of the median motor, median sensory, and sural nerves of the smelter workers were slowed for the unstandardized values. Table 6-4 shows the same analyses computed on the standardized NCV values adjusted for age and temperature; slowing was found in sensory nerves only. When the correlation between NCV values and years of employment was computed, median motor NCV slowing was seen to be associated with increasing years of employment (Table 6-5). Since the exact pattern of early sensory and later motor nerve effects were found in a previously studied lead-exposed group (Singer, Valciukas and Lilis, 1982), the study group was divided at intervals of 10 years of employment to examine the problem in more detail. For comparison purposes, the t -test analyses of the smelter workers and the lead-exposed automobile workers will be presented in Tables 6-6 and 6-7. At less than 10 years employment, both exposed groups showed slowing of the sensory nerves (but not motor nerves) (Table 6-6). Slowing of the median motor NCV was found in smelter workers employed more than 15 years, and in automobile assembly workers at 10 years. The earlier onset of motor slowing among automobile assembly workers may be due to their higher levels of lead exposure.

The correlational analyses of Pb-B, ZPP and As-U with NCV was performed on the smelter workers divided into two groups: less than or greater than 15 years employment. The smelter workers were divided at 15 years of employment because the differential pattern of early sensory and later motor nerve effects found among automobile assembly workers had been also observed among copper smelter workers. NCV slowing was associated with increased ZPP levels in both duration groups ($r = -0.30$, $p < 0.08$, $N = 35$; $r = -0.20$, $p < 0.06$, $N = 83$, respectively). Pb-B and As-U levels were not

Table 6-3: Mean nerve conduction velocities (NCV) of exposed versus control groups

<u>NERVE</u>	<u>GROUP</u>	<u>N</u>	<u>MEAN NCV (m/s)</u>	<u>STD. DEV.</u>	<u>t</u>	<u>Probability</u>
Median Motor						
Lead and arsenic-exposed		119	54.3	6.31	2.49	0.01
Controls		26	57.6	5.20		
Median Sensory						
Lead and arsenic-exposed		119	39.9	5.65	5.63	<0.0001
Controls		24	46.8	4.47		
Peroneal Motor						
Lead and arsenic-exposed		101	47.4	4.78	2.28	0.20
Controls		13	49.2	5.81		
Sural						
Lead and arsenic-exposed		103	34.9	2.78	6.93	<0.0001
Controls		20	42.8	4.90		

6-4: Mean standardized nerve conduction velocities of exposed versus control group^a

<u>NERVE</u>	<u>GROUP</u>	<u>N</u>	<u>MEAN NCV (m/s)</u>	<u>STD. DEV.</u>	<u>t</u>	<u>Probability</u>
Median Motor						
	Lead and arsenic-exposed	119	0.70	2.22	0.44	0.66
	Controls	25	0.91	1.70		
Median Sensory						
	Lead and arsenic-exposed	119	-1.31	1.41	5.95	<0.0001
	Controls	23	-0.04	0.81		
Peroneal Motor						
	Lead and arsenic-exposed	101	3.17.	1.86	1.27	0.21
	Controls	12	2.43	1.14		
Sural						
	Lead and arsenic-exposed	103	-2.72	0.96	5.85	<0.0001
	Controls	20	0.52	1.62		

^aBased upon Z values which represent the subtraction of velocity expected on the basis of age from the temperature corrected velocity divided by the standard error of estimate.

Table 6-5: Correlation of years of employment (mean = 12.0 years) with standardized nerve conduction velocities^a (NCV) in copper smelter workers.

	<u>Median motor</u> ^b	<u>Median sensory</u>	<u>Peroneal motor</u>	<u>Sural</u>
r	-0.24	-0.01	-0.17	0.02
probability	0.01	0.92	0.11	0.82
N	107	109	93	95

^aBased upon Z values which represent the subtraction of the velocity expected on the basis of age from the temperature corrected observed velocity divided by the standard error of estimate.

^bThis value was -0.42, $p < 0.01$, $n = 37$ in automobile assembly workers.

Table 6-6: Mean standardized nerve conduction velocities (NCV) of copper smelter employees and automobile assembly workers exposed for less than 10 years versus control group^a

NERVE	GROUP	N	MEAN NCV (m/s)	STD. DEV.	t	Probability
Median Motor						
	Lead-exposed	24	1.11	1.88	0.39	0.70
	Lead and arsenic exposed	62	0.99	2.46	0.31	0.76
	Controls	25	0.91	1.70		
Median Sensory						
	Lead-exposed	24	-0.94	1.24	2.94	0.005
	Lead and arsenic-exposed	62	-1.33	1.47	5.64	<0.0001
	Controls	23	-0.04	0.81		
Peroneal Motor						
	Lead-exposed	15	2.68	1.14	0.36	0.72
	Lead and arsenic-exposed	55	3.22	1.56	1.47	0.15
	Control	12	2.43	2.14		
Sural						
	Lead-exposed	15	-2.42	0.86	4.46	<0.0001
	Lead and arsenic-exposed	56	-2.85	0.98	6.69	<0.0001
	Controls	20	-0.52	1.63		

^aBased upon Z values which represent the subtraction of the velocity expected on the basis of age from the temperature corrected velocity, divided by the standard error of estimate.

Table 6-7: Mean standardized nerve conduction velocities (NCV) of copper smelter employees and automobile assembly workers exposed more than 10 years versus control group^a

NERVE	GROUP	N	MEAN Z-VALUE	STD. DEV.	t	Probability
Median Motor						
	Lead-exposed	13	-0.62	1.94	2.51	0.02
	Lead and arsenic exposed ^b	57	0.51	1.96	0.77	0.44
	Lead and arsenic-exposed ^b	36	-0.15	1.70	2.29	0.03
	Controls	25	0.91	1.70		
Median Sensory						
	Lead-exposed	11	-1.23	0.96	3.76	0.0007
	Lead and arsenic-exposed	58	-1.40	1.01	6.42	<0.0001
	Controls	23	-0.04	0.81		
Peroneal Motor						
	Lead-exposed	10	2.62	2.21	0.20	0.85
	Lead and arsenic-exposed	47	3.23	1.89	1.27	0.21
	Control	12	2.43	2.14		
Sural						
	Lead-exposed	9	-2.69	1.09	3.36	0.001
	Lead and arsenic-exposed	48	-2.62	0.90	6.01	<0.0001
	Controls	20	-0.52	1.63		

^aBased upon Z values which represent the subtraction of the velocity expected on the basis of age from the temperature corrected velocity, divided by the standard error of estimate.

^bExposed more than 15 years.

correlated with NCV in either group. The interaction factor of ZPP multiplied by As-U did not increase the strength of the correlation between NCV and ZPP alone.

Although subjects were not tested if they reported consuming more than 28 alcoholic beverages per week, it was still possible that alcohol consumption could have been related with NCV slowing in the group examined. A composite alcohol index was constructed by adding the number of servings reported for an average week, multiplying this number by the subject's age minus the age he started drinking, and dividing this product by the subject's weight. Correlation coefficients were computed comparing standardized NCV values with the alcohol index, and no correlation was found.

Table 6-8 shows the prevalence of NCV slowing by Pb-B group, comparing copper smelters (exposed to arsenic and lead) with automobile assembly workers (exposed to lead only). For the smelter workers, 60% of those whose Pb-B level was less than 40 $\mu\text{g}/\text{dl}$ had slowing in the median sensory or sural nerves, compared with 20% of the automobile assembly workers; for those whose blood lead was 40-59 $\mu\text{g}/\text{dl}$, the prevalence was 70% and 35%, respectively. Prevalence of slowing in the motor nerves was too infrequent for comment. Overall, 61% of the smelter workers versus 40% of the automobile assembly workers had NCV slowing. This suggests that arsenic exposure may be a factor in the NCV changes observed.

Discussion

Early slowing of the sensory nerves was found in copper smelter workers exposed to arsenic and lead, followed by slowing of motor NCV after 15 years exposure. This finding is consistent with previous reports of arsenic exposure and neuropathy. A pattern of NCV slowing can be seen which is similar to that found among workers exposed to lead only.

A question remains as to the relative contribution of lead and arsenic to NCV slowing in copper smelter workers. As for lead, ZPP levels were correlated with median motor NCV, indicating that lead exposure is a factor in the PNS deficits found. Correlation of NCV with urinary arsenic was not

Table 6-8: Prevalence of nerve conduction velocity slowing in copper smelter workers compared with automobile assembly workers by blood lead levels.

Sensory Nerves

	<u>Copper Smelters</u>	<u>Automobile Assembly Workers</u>
Pb-B ($\mu\text{g}/\text{dl}$)	Number slowed within subgroup, percentage.	
<40	56/94 (60%)	1/4 (20%)
40-59	21/30 (70%)	6/17 (35%)
60-79	0/0	4/12 (33%)
80+	0/0	5/6 (83%)

Motor Nerves

<40	3/91 (3%)	0/5 (0%)
40-59	3/27 (10%)	2/17 (5%)
60-79	0/0 (0%)	1/11 (8%)
80+	0/0 (0%)	0/6 (0%)

found. It is possible that urinary arsenic levels may not have been sufficiently elevated to demonstrate quantitative effects of long-term exposure to arsenic.

The levels of lead exposure as measured by Pb-B were lower in copper smelter workers than in automobile assembly workers, as seen in Table 6-8. However, the prevalence of NCV slowing was higher among copper smelter workers, indicating a possible role of arsenic exposure in the NCV deficits.

Summary

Copper smelter workers are exposed to inorganic lead and arsenic which are present in copper ores. Both can adversely affect many body systems, including the peripheral nervous system (PNS). Nerve conduction velocity assessment (NCV) provides an objective and accurate indicator of PNS function. Conduction velocities of the median motor, median sensory, peroneal motor, and sural nerves were assessed in 127 copper smelter workers. Mean age was 42 years and mean duration of employment was 12. Mean blood lead was 32.8 $\mu\text{g}/\text{dl}$, and mean urine arsenic was 33.9 $\mu\text{g}/\text{l}$. After standardization for age and temperature, mean NCV slowing was found in the median sensory and sural nerves ($p < 0.001$ in both). Slowing in median motor NCV was correlated with years of employment ($r = -0.24$, $p < 0.01$). Mean NCV slowing of the median motor nerve was found in workers exposed more than 15 years. A time course of PNS effects is noted, where sensory NCV seems slowed before motor NCV.

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CHAPTER VII

Pulmonary function studies on copper smelter workers and miners:
Comparison with similar studies in a general population

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A. Introduction

The effects on the lungs of various agents to which the smelter workers are exposed were evaluated by medical history, respiratory questionnaire, physical examination, chest roentgenography and pulmonary function tests. The latter consisted of:

1. The conventional spirometric measurements, forced vital capacity (FVC) and forced expiratory volume - 1 second (FEV_1) which detect and separate restrictive and obstructive impairment;
2. Forced expiratory flow over the mid-vital capacity ($FEF_{25-75\%}$) which detects earlier changes in air flow (small airways obstruction);
3. Maximum expiratory flow-volume curves were obtained, allowing instantaneous flow rates to be measured at mid- and low-lung volumes. These may be more sensitive indicators of small airway obstruction and will be considered in a future report.

B. Materials and Methods

Standard spirometric measurements, (FVC and FEV_1 and $FEF_{25-75\%}$), were performed using an automated (12L) rolling-seal spirometer (Gould Medical Instruments, Dayton, Ohio). At least three efforts which met the specifications of the Epidemiology Standardization Project¹ were obtained. Values were calculated from the "best curve" having the largest sum of FVC and FEV_1 .

Occupational groups were defined as:

- Active copper smelter employees
- Retired copper smelter employees
- Miners (see Chapter I).

All subjects were white, eliminating the racial variable in spirometric results.

Smoking groups were defined as:

- Non-smokers - never smoked or smoked < one cigarette/day, or smoked \leq 10 cigarettes/day for < 6 months.
- Current smokers - exceeded the limits defined above, and were smoking at the time of examination, and
- Ex-smokers (discontinued \leq 2 years ago).

C. Results

1. Linear Regression Equations

Routine spirometric measurements were described by a standard linear regression model:

(Observed Spirometric Value = $a(\text{Ht}) + b(\text{age}) + C$) for each occupational and smoking group, as defined above. Most of the analysis will concern itself with the active smelter workers, who were the largest group.

The regression equations for the three spirometric measurements in active smelter workers are shown in Table 7-1.

The r^2 values of the equations for FVC and FEV_1 range from 0.52 to 0.61 and for $\text{FEF}_{25-75\%}$ from 0.26 - 0.44. These are similar to r^2 values of most well done large studies.

In the large group of active copper smelter workers, spirometric function declined with age in all smoking categories, but more so in the two groups with a positive smoking history. This is seen in the larger age coefficients for current and ex-smokers. Differences were most notable for FEV_1 and $\text{FEF}_{25-75\%}$, as expected. Older smokers demonstrated the lowest observed value for FVC, FEV_1 , and $\text{FEF}_{25-75\%}$; values of ex-smokers were intermediate between those of non-smokers and those of current smokers. These findings are expected in any large population.

Table 7 - 1

Linear regression equations for spirometric measurements
in active copper smelter workers by smoking history

	<u>a (Height, in)</u>	<u>b (Age, yrs)</u>	<u>c (Constant)</u>
<u>SMOKERS</u>			
FVC	0.12	-0.04	-2.06
FEV ₁	0.07	-0.04	0.35
FEF _{25-75%}	0.02	-0.06	4.15
<u>EX-SMOKERS</u>			
FVC	0.15	-0.04	-3.15
FEV ₁	0.10	-0.05	-1.04
FEF _{25-75%}	0.06	-0.05	1.09
<u>NON-SMOKERS</u>			
FVC	0.15	-0.03	-3.77
FEV ₁	0.08	-0.03	-0.66
FEF _{25-75%}	0.04	-0.04	2.48

In Figures 7-1 - 7-3, the regression equations for the three smoking categories are plotted for each spirometric measurement against age; height is set at 180 cm.

2. Correlations of spirometric measurements with cadmium burden, smoking burden, age, and duration of employment.

Utilizing these regression equations as predictors of spirometric performance, we searched for trends and correlations within work groups related to duration of employment, pack-years of smoking, age, cadmium body burden (as reflected in urinary Cd microgram/g creatinine), and a number of independent variables.

a. Duration from onset of employment

The $FEF_{25-75\%}$ is considered to be a sensitive measurement of obstruction in the small airways, expressing the measurement as percent of that predicted adjusted for the expected effect of age. The active and retired copper smelter workers, but not the miners, showed a decrease in $FEF_{25-75\%}$ (expressed as percentage of the predicted reference value for non-smokers) as their time from onset of employment increased. This is shown in Figure 7-4, as percent of predicted $FEF_{25-75\%}$ against duration from onset of employment for the three occupational groups. Figure 7-4A shows percent of predicted $FEF_{25-75\%}$ against duration of employment for active smelter workers by smoking category. There is a negative correlation even in non-smokers.

Loss of FVC and FEV_1 (similarly expressed as percent of the predicted value) was not related to duration since onset of employment.

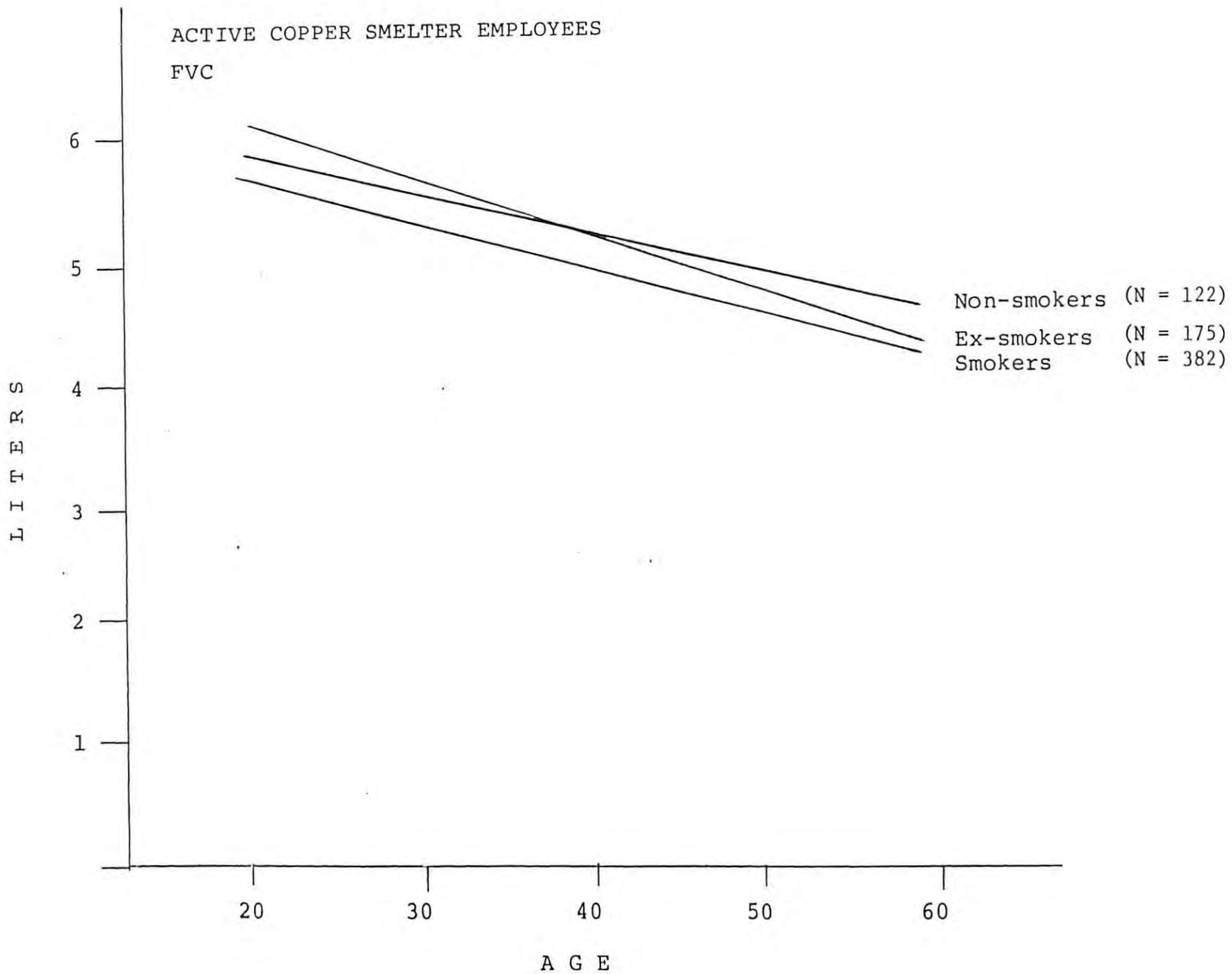


Figure 7 - 1: Linear regression of the spirometric measurement FVC against age in active copper smelter employees; height is fixed at 180 cm.

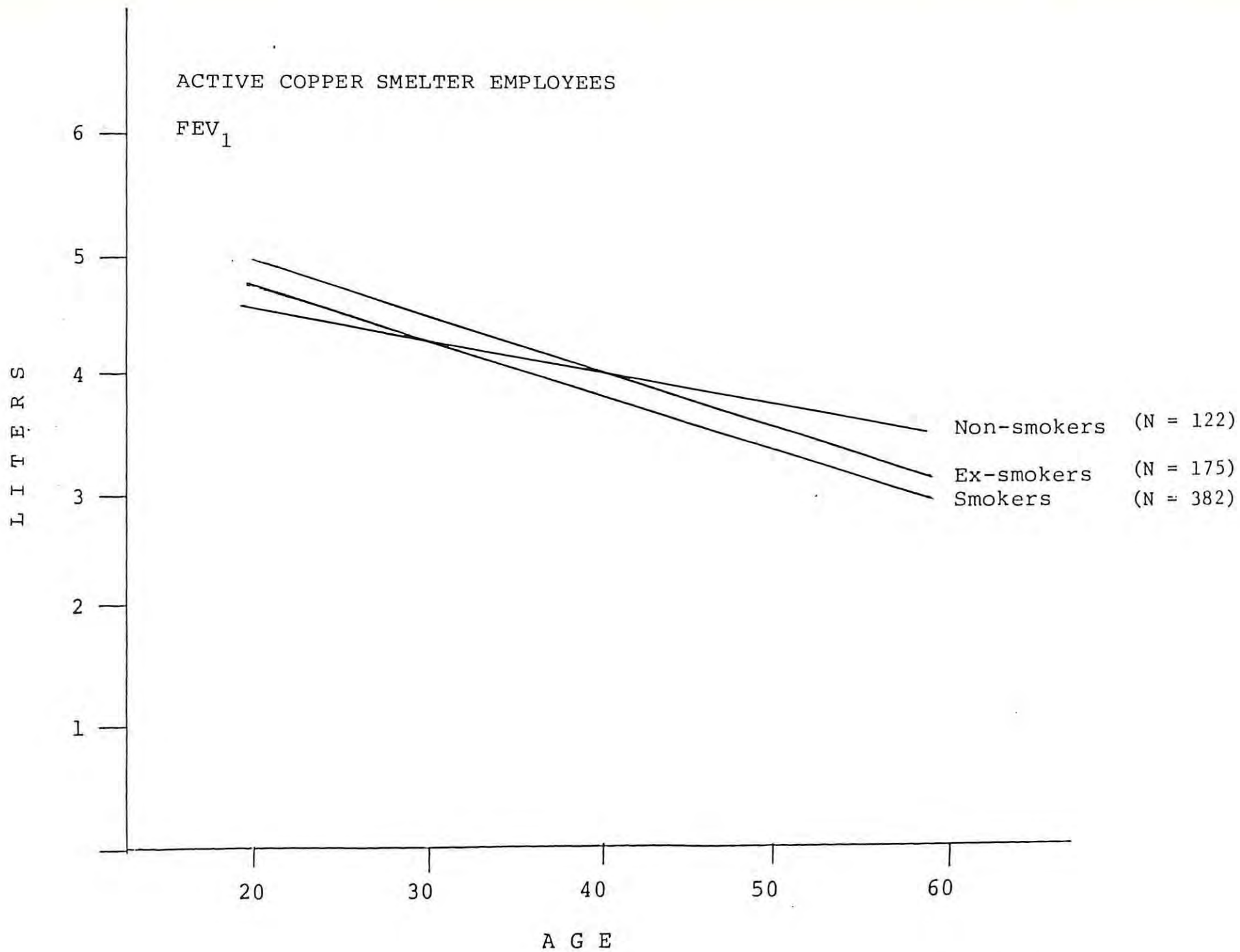


Figure 7 - 2: Linear regression of the spirometric measurement FEV₁ against age in active copper smelter employees; height is fixed at 180 cm.

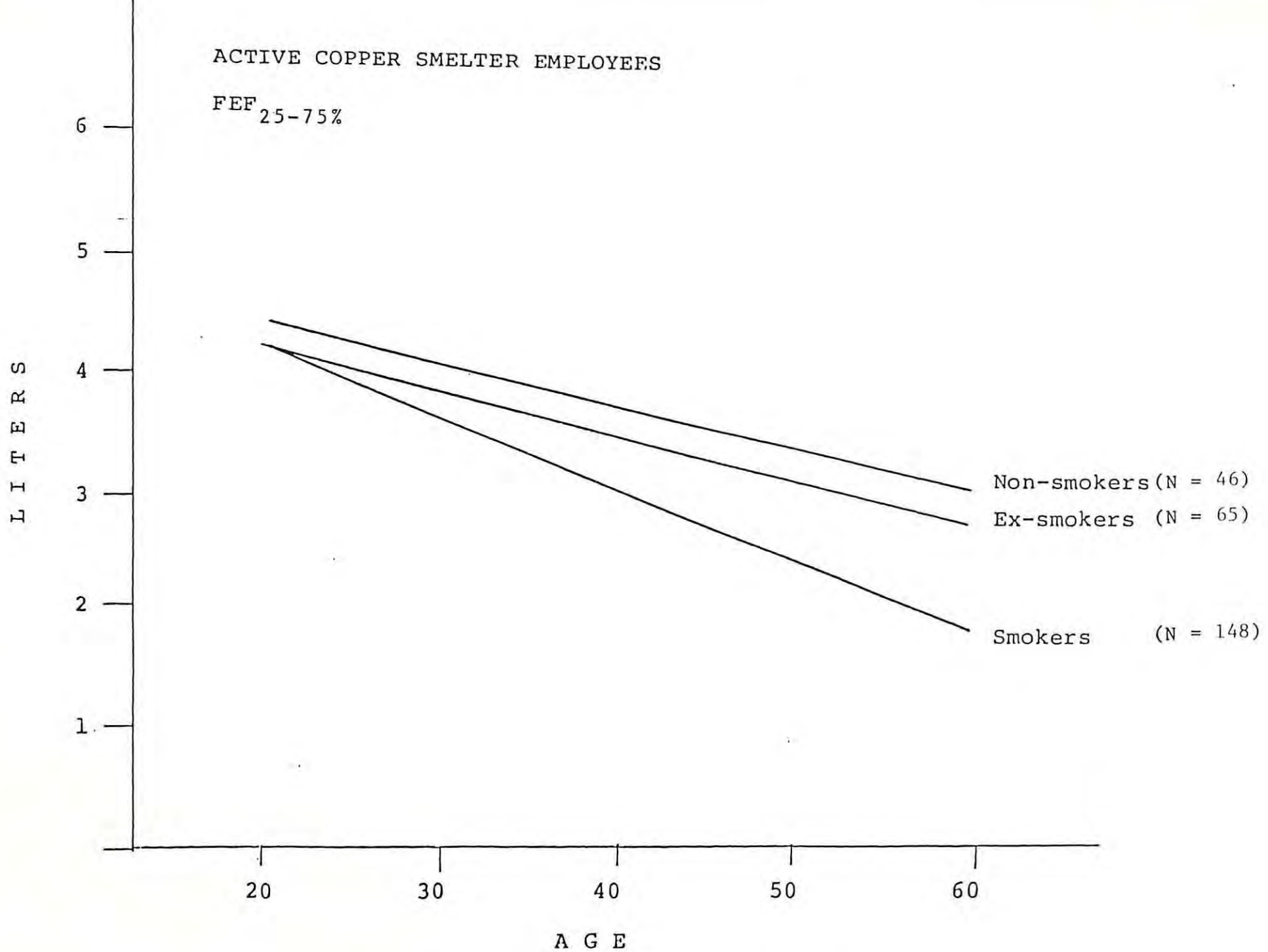


Figure 7-3: Linear regression of the spirometric measurement FEF_{25-75%} against age in active copper smelter employees; height is fixed at 180 cm.

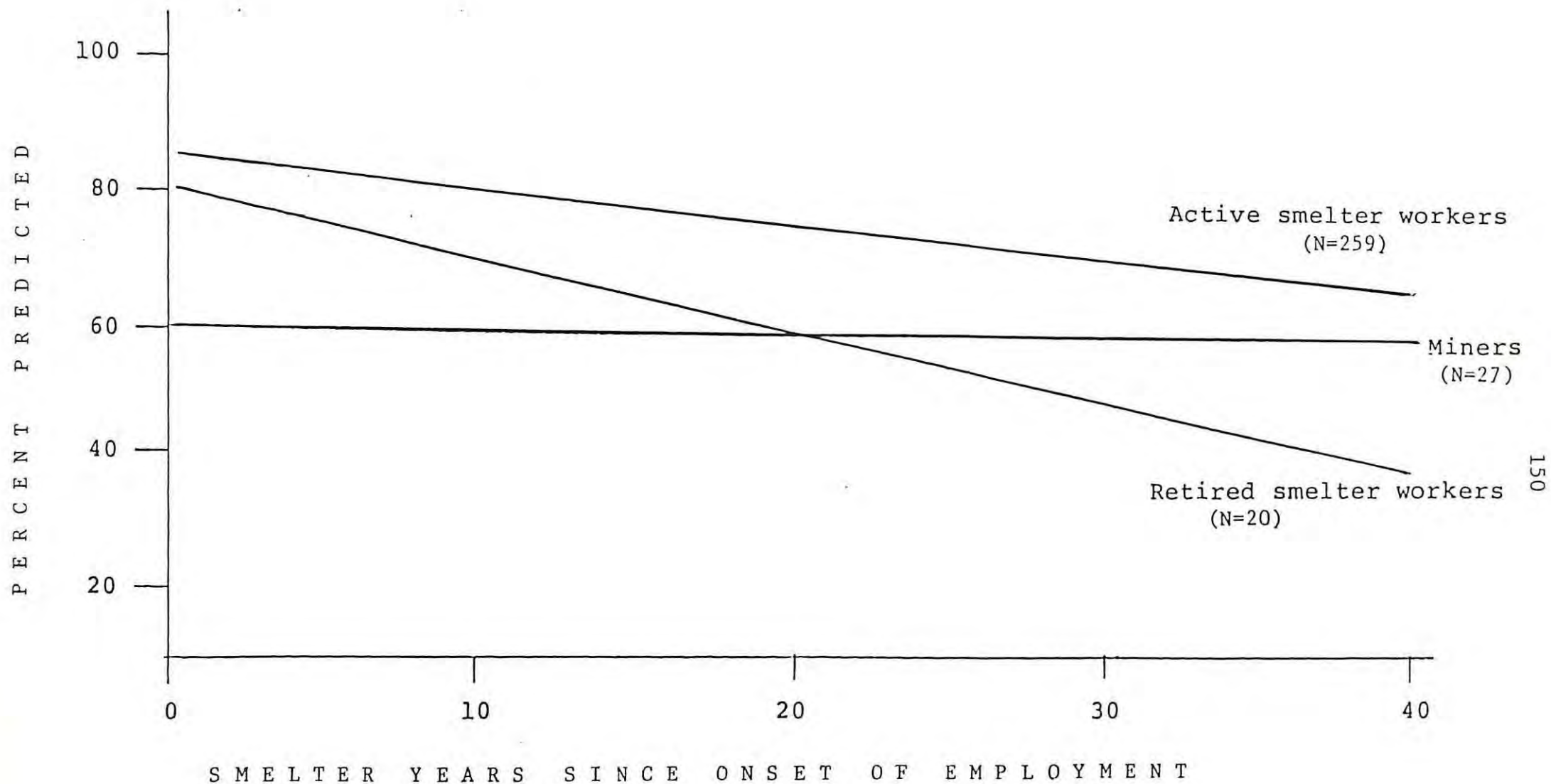


Figure 4.

The spirometric measurement $FEF_{25-75\%}$ expressed as mean per cent of value predicted for each occupational group plotted against number of years since onset of employment for active and retired copper smelter workers and miners.

ACTIVE COPPER SMELTER EMPLOYEES

FEF₂₅₋₇₅

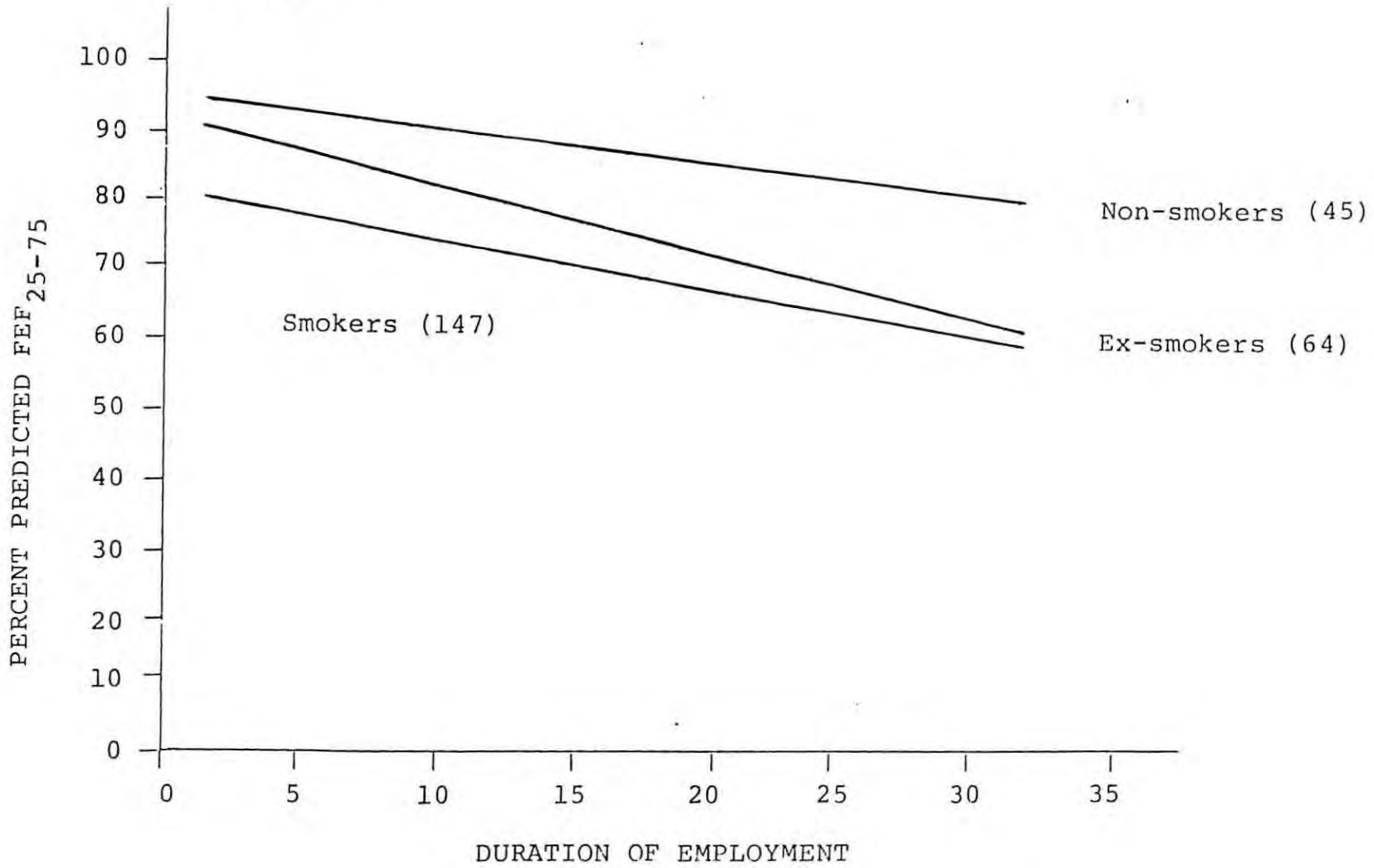


Figure 7-4A : Per cent predicted FEF₂₅₋₇₅ plotted against duration of employment for active copper smelter workers. Note the negative correlation for all smoking categories, including non-smokers.

b. Cadmium body burden

Spirometric measurements showed significant correlations ($p < 0.0001$) with urinary Cd $\mu\text{g/g}$ creatinine (Cd-U). Of the five variables listed below (as well as numerous other variables not listed), the variable Cd-U exhibited the strongest correlation with percent predicted FVC and percent predicted FEV₁. Correlation with MMF was suggested but did not reach statistical significance, most likely because of the greater inherent variability on this measurement, and the smaller number of people who performed the test.

All of the following variables;

- Cd-U,
- Cd-B (serum creatinine),
- Smelter years,
- Pack-years,
- Age,

correlated with each other.

Additional analysis was performed for the active smelter workers. The most significant single correlation of Cd-U was with Cd-B, as might be expected. The next most significant correlation of Cd-U was with smelter years (for non-smokers), pack-years (for ex-smokers), and age (for smokers).

Mean values for these variables are shown in Table 7-2. Figure 7-5 summarizes the variables of age, smelter years, and smoking duration for active smelter workers.

The cadmium burden, as reflected in Cd-U, arises from cadmium exposure in the smelter and from Cd known to be present in cigarette tobacco. Mean Cd-U levels by smoking category among active smelter workers varied with the smoking history, as shown in Table 7-2.

Table 7 - 2

Mean values for age (years), pack-years, duration of employment (years), and urinary cadmium $\mu\text{g/g}$ creatinine (Cd-U) in active smelter workers

	<u>N</u>	<u>Age</u>		<u>Pack-years</u>		<u>Duration</u>		<u>Cd-U</u> *	
		<u>Mean</u>	<u>\pm SD</u>	<u>Mean</u>	<u>\pm SD</u>	<u>Mean</u>	<u>\pm SD</u>	<u>Mean</u>	<u>\pm SD</u>
Smokers	382	42.2	12.9	28.1	19.5	12.0	9.5	1.43	1.17
Ex-smokers	175	45.6	11.8	30.7	24.9	12.9	9.2	0.98	0.75
Non-smokers	122	41.0	12.9	0	0	10.7	8.4	0.58	0.48

* Means are for subjects for whom all data in table are available.

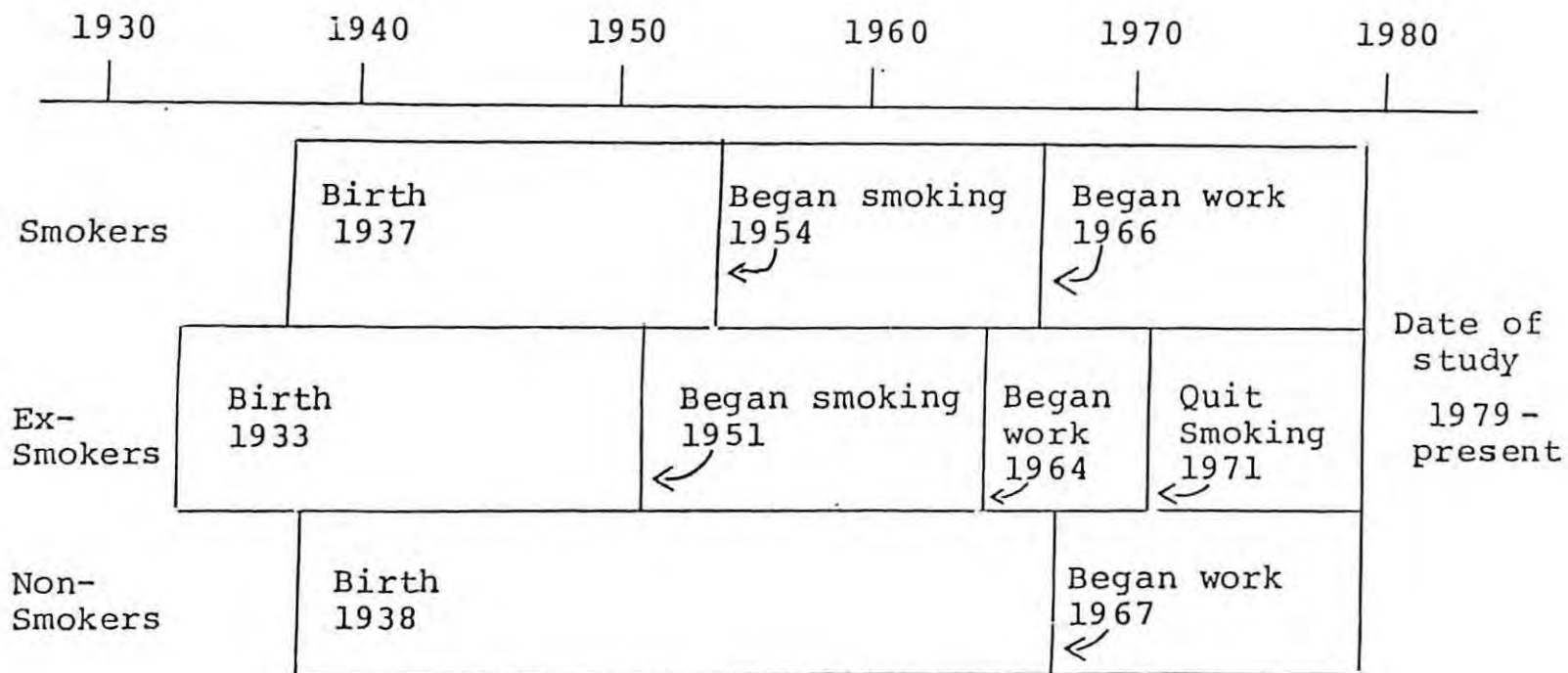


Figure 7-5

Bar graph showing age, duration of smoking, and duration from beginning work for active copper smelter employees.

Mean values for the three spirometric measurements and for urinary Cd are shown for active and retired smelter workers and for miners in Tables 7-3 - 7-5.

Figures 7-6 - 7-8 show mean FVC, FEV₁, and FEF_{25-75%} (respectively) plotted against urinary cadmium for the three occupational categories. A strong inverse relationship was noted between the three spirometric measurements and urinary cadmium for active and retired smelter workers, but not for miners. When active smelter workers were categorized by smoking history, the relationships were significant ($p < 0.05$) for all spirometric tests and all smoking groups except FEF_{25-75%} in non-smokers, whose number was small (37). Looking at FEV₁ in non-smokers (available on 110 workers) the p value was < 0.014 .

Spirometric measurements (expressed as mean percent predicted) for active smelter workers above the median value for urinary Cd $\mu\text{g/g}$ creatinine were compared with spirometric measurements for workers below the median value for urinary Cd (Table 7-6). The median value was chosen because the workers with high values influenced the mean Cd-U disproportionately to their number. Values for FVC, FEV₁, and FEF_{25-75%} of both current and ex-smokers were lower in those whose urinary Cd was above the median. This confirmed the correlation noted between spirometric performance and cadmium burden. However, the relative contributions of occupational exposure and smoking cannot be segregated since both mean pack-years and mean duration of employment were higher in those above the median Cd-U.

For non-smokers, there was no difference in FVC or FEV₁, but the difference in FEF_{25-75%} between those with high and those with low values for Cd-U was even greater than for workers with a history of smoking. Thus, in workers whose only cadmium exposure was occupational, the higher the body burden of Cd, the lower was this sensitive measurement of lung function.

Table 7 - 3

Mean FVC (expressed as per cent predicted)
and urinary cadmium $\mu\text{g/g}$ creatinine for
active and retired smelter workers and miners

		N*	Mean FVC \pm SD	Mean urinary cadmium/ $\mu\text{g/g}$ creatinine \pm SD
Active smelter workers	Smokers	330	96.9 \pm 14.8	1.43 \pm 1.17
	Ex-smokers	154	100.4 \pm 13.8	0.98 \pm 0.57
	Non-smokers	110	102.3 \pm 14.6	0.58 \pm 0.48
Retired smelter workers	Smokers	27	93.3 \pm 20.5	2.19 \pm 1.40
	Ex-smokers	27	85.0 \pm 20.3	1.15 \pm 0.91
	Non-smokers	11	92.7 \pm 15.6	0.34 \pm 0.23
Miners	Smokers	52	94.5 \pm 19.6	1.69 \pm 1.10
	Ex-smokers	41	89.0 \pm 19.3	1.1 \pm 1.00
	Non-smokers	17	97.0 \pm 14.0	0.48 \pm 0.45

* Refers to subjects for whom both spirometric data and urinary cadmium corrected for creatinine levels are available.

Table 7-4

Mean FEV₁ (expressed as per cent predicted)
and urinary cadmium $\mu\text{g/g}$ creatinine for active
and retired copper smelter workers and miners

		N*	Mean FEV ₁ \pm SD	Mean urinary cadmium $\mu\text{g/g}$ creatinine \pm SD
Active smelter employees	Smoker	330	95.0 \pm 17.6	1.43 \pm 1.17
	Ex-smoker	154	100.9 \pm 16.4	0.98 \pm 0.75
	Non-smoker	110	105.1 \pm 15.4	0.58 \pm 0.48
Retired smelter employees	Smoker	27	85.1 \pm 24.1	2.20 \pm 1.40
	Ex-smoker	27	82.9 \pm 26.3	1.15 \pm 0.91
	Non-smoker	11	98.2 \pm 16.4	0.34 \pm 0.23
Miners	Smoker	52	90.5 \pm 21.2	1.69 \pm 1.05
	Ex-smokers	41	86.1 \pm 27.8	1.10 \pm 1.00
	Non-smokers	17	104.5 \pm 14.2	0.48 \pm 0.45

* Refers to subjects for whom both spirometric data and urinary cadmium corrected for creatinine levels are available.

Table 7 - 5

Mean FEF_{25-75%} (expressed as per cent predicted)
and urinary cadmium $\mu\text{g/g}$ creatinine for active
and retired copper smelter workers and miners

		N *	Mean FEF _{25-75%} \pm SD	Mean urinary cadmium $\mu\text{g/g}$ creatinine \pm SD
Active smelter workers	Smokers	133	73.8 \pm 28.1	1.54 \pm 1.46
	Ex-smokers	59	83.3 \pm 38.5	1.13 \pm 0.90
	Non-smokers	37	87.5 \pm 27.4	0.63 \pm 0.55
Retired smelter workers	Smokers	6	49.9 \pm 17.1	1.44 \pm 0.64
	Ex-smokers	7	72.5 \pm 33.9	0.70 \pm 0.47
	Non-smokers	2	86.9 \pm 39.5	0.30 \pm 0.17
Miners	Smokers	15	53.2 \pm 26.0	1.57 \pm 0.95
	Ex-smokers	5	59.1 \pm 29.6	0.38 \pm 0.12
	Non-smokers	4	91.5 \pm 35.1	0.74 \pm 0.78

*Refers to subjects for whom both spirometric data and urinary cadmium levels corrected for creatinine are available.

Table 7 - 6

Spirometric values (expressed as per cent predicted)
for active copper smelter workers above and below the
median total body cadmium burden (expressed as urinary
Cd $\mu\text{g/g}$ creatinine)

		<u>\leq median value</u>	<u>$>$ median value</u>
<u>Smokers</u>	Cd-U	0.51	2.05
	Cd-B	6.23	7.55
	FVC	99.0	95.2
	FEV ₁	98.4	92.3
	FEF _{25-75%}	81.9	67.5
<u>Ex-smokers</u>	Cd-U	0.48	1.66
	Cd-B	1.19	1.77
	FVC	102.0	97.2
	FEV ₁	102.1	97.4
	FEF _{25-75%}	88.4	75.7
<u>Non-smokers</u>	Cd-U	0.39	1.40
	Cd-B	0.81	2.10
	FVC	102.8	103.0
	FEV ₁	105.6	106.2
	FEF _{25-75%}	94.9	73.8

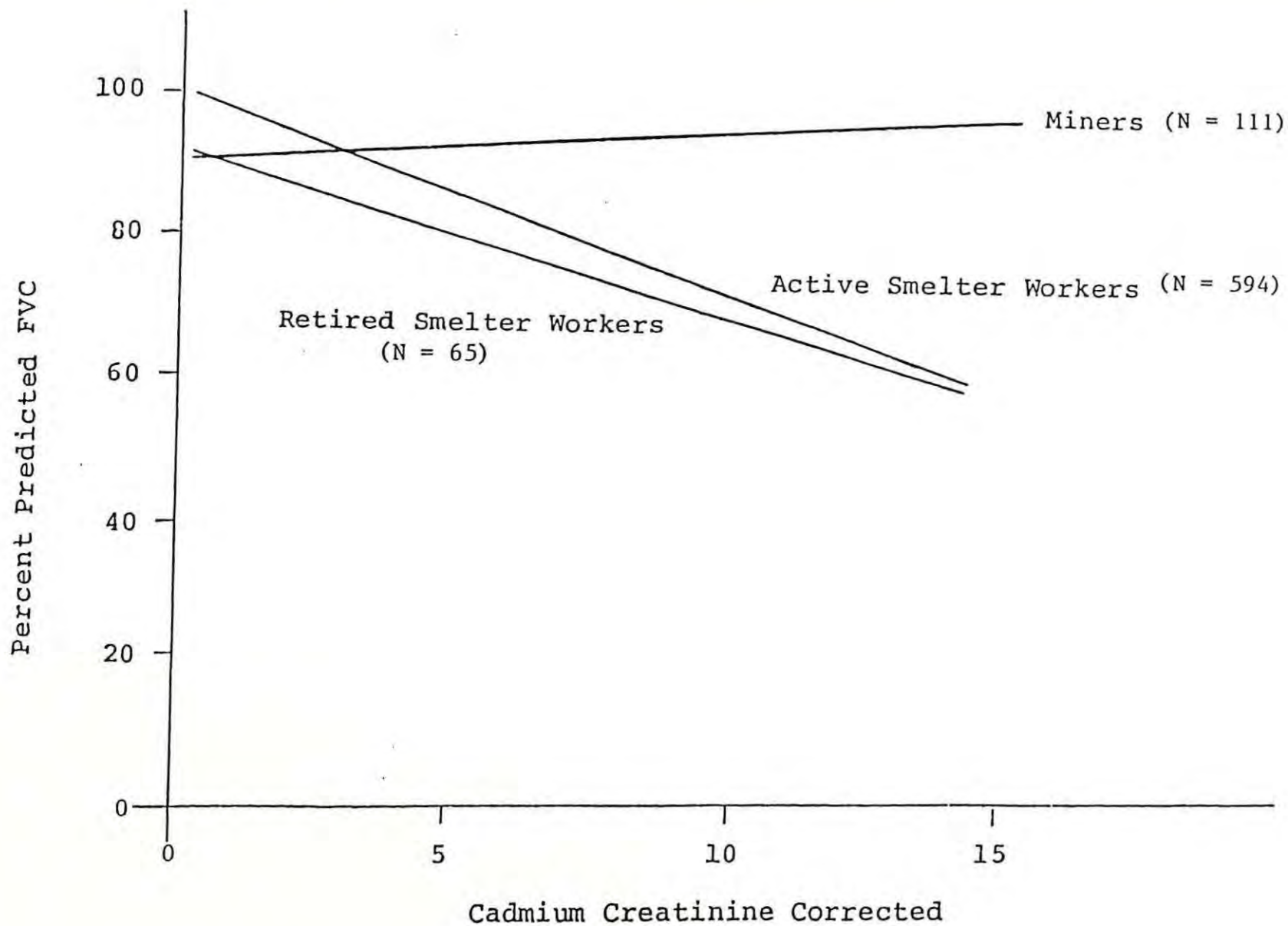


Figure 7-6

The FVC expressed as per cent predicted plotted against cadmium burden expressed as urinary cadmium $\mu\text{g/g}$ creatinine for all three occupational groups.

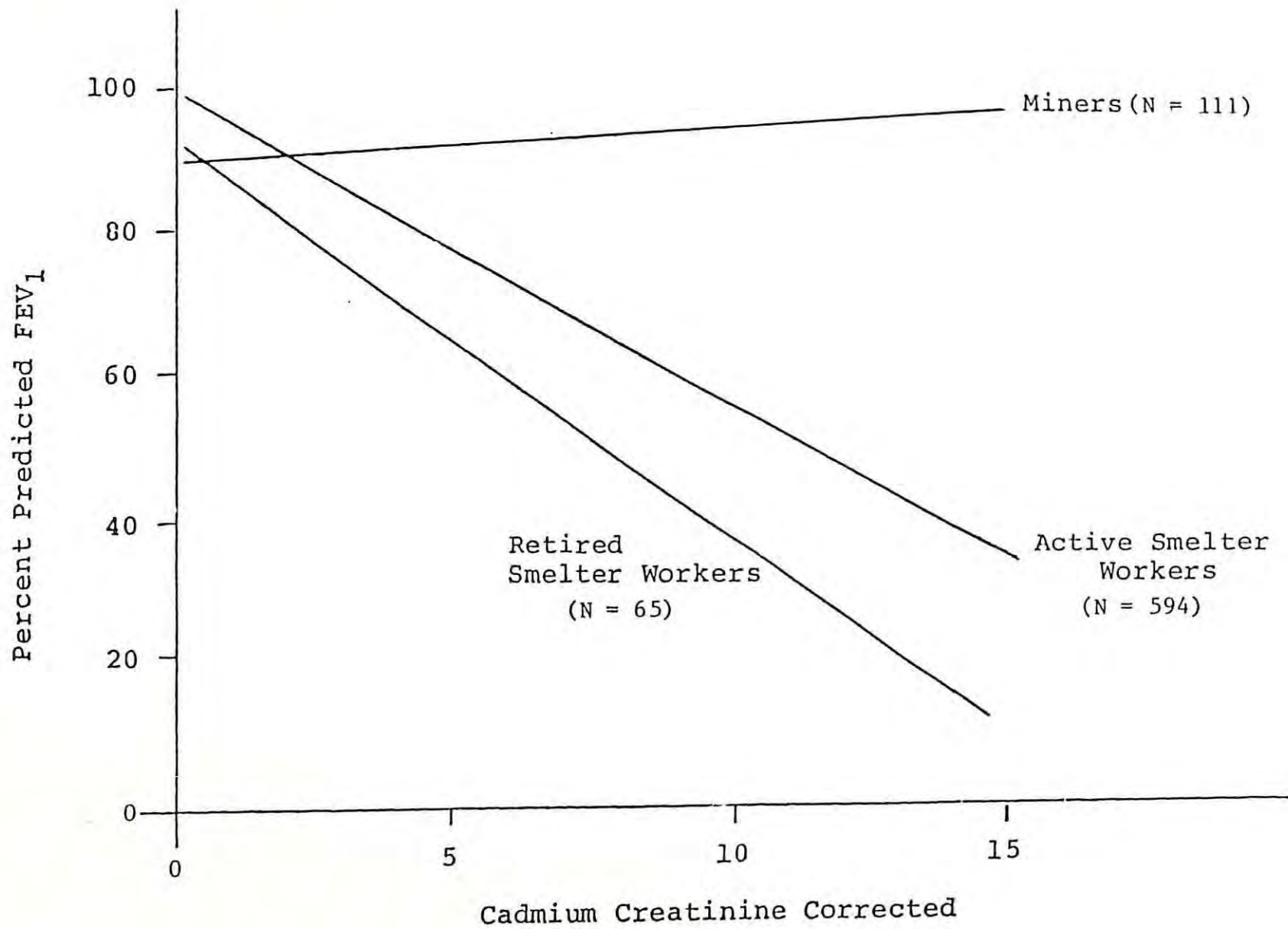


Figure 7-7

The FEV₁ expressed as per cent predicted plotted against cadmium burden expressed as urinary cadmium $\mu\text{g/g}$ creatinine for all three occupational groups.

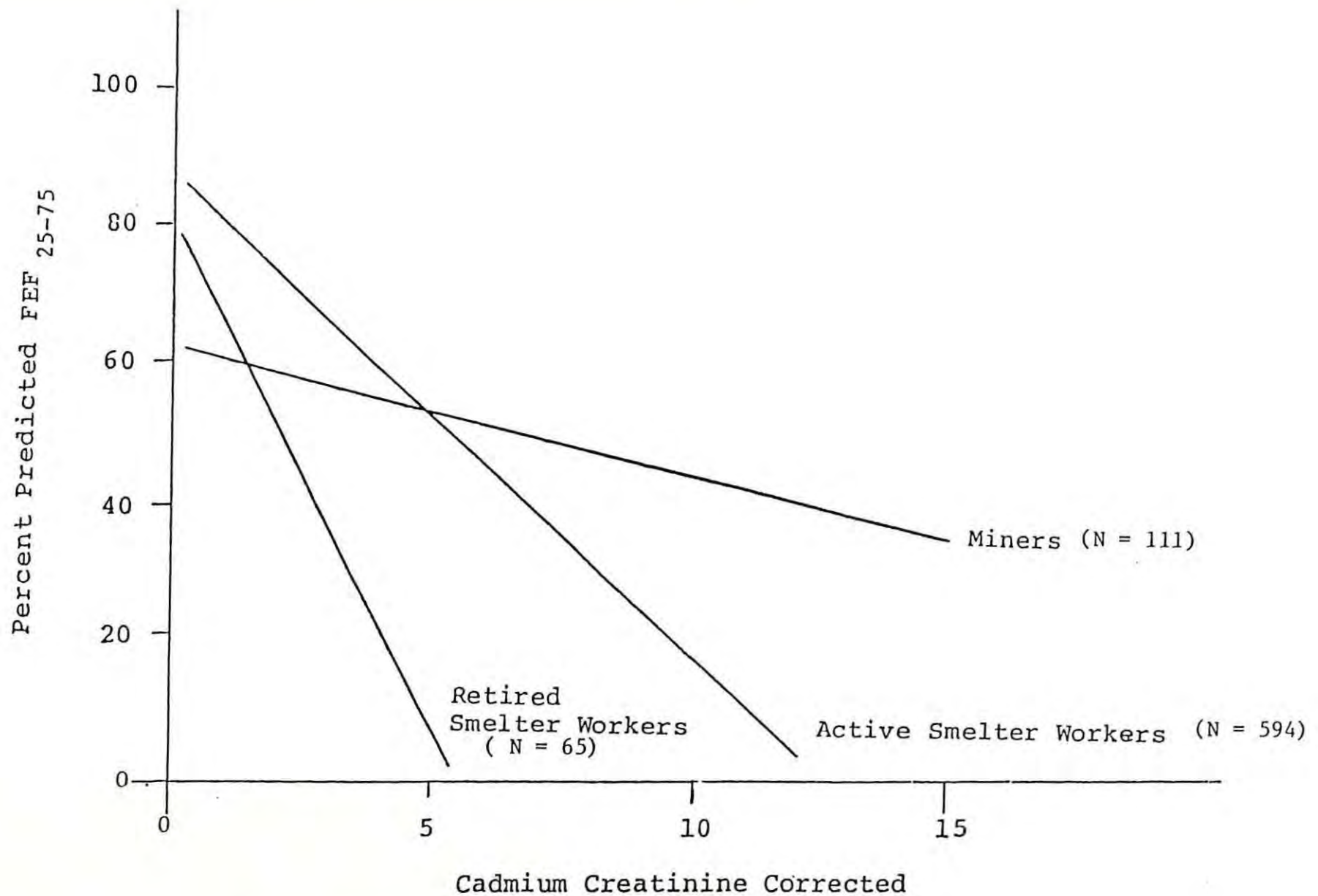


Figure 7 - 8

The FEF_{25-75%} as per cent predicted plotted against cadmium burden expressed as urinary cadmium µg/g creatinine for all three occupational groups .

By examining the correlations between the different variables, Cd-U in non-smokers was best explained by years in the smelter ($r = 0.41$, $p < 0.0001$). The effect of age ($r = 0.40$, $p < 0.0001$) predominated over the effects of years in the smelter ($r = 0.26$, $p < 0.0001$) and pack-years ($r = 0.33$, $p < 0.0001$) when current and ex-smokers were combined. The relative contributions of duration of exposure to the smelter environment and of cigarette burden can not be easily separated. In ex-smokers, the effects of pack-years predominated over that of age and/or smelter years, suggesting that in this group, cigarette smoking best explained the cadmium burden.

D. Comparison with a general population

To better understand the effects of working in a copper smelter on spirometric performance, we compared the data obtained from copper smelter workers with spirometric observations from a large number of white male subjects, a representative sample randomly selected from the general population (Michigan, $N = 595$). The latter is the only study of spirometric performance based on an entire populous state or province. (The population of Michigan at the time of the study was approximately 9,000,000.) Both studies utilized similar laboratory techniques and technical staff. The two populations differed only with respect to age and smoking history, as discussed below. The Michigan males were a cross-section of the general population and not an ideal comparison group for smelter workers and miners. They were utilized because a manual or industrial working population unexposed to specific respiratory hazards and studied in a similar way was not available, while the Michigan population included many blue collar workers, while others were engaged in "white collar" occupations (lawyers, teachers, etc.).

Data on smoking history are shown in Tables 7-7 and 7-8, and on age in Table 7-8. Smoking smelter workers were 6.7 years older than smoking males from Michigan. There were 14% more men with a smoking history among the smelter workers. Both current and ex-smokers in Noranda had

Table 7 - 7

Distribution of smoking habits among active copper smelter workers
(Noranda) and a comparison general population (Michigan males)

	<u>Active smelter workers</u>	<u>All Noranda workers</u>	<u>Michigan</u>
Smokers	56%	54%	44%
Ex-smokers	26%	29%	25%
Non-smokers	18%	17%	31%

Table 7 - 8

Mean spirometric values in all Noranda employees
and in the comparison general population (Michigan)

	<u>Smokers</u>		<u>Non-smokers</u>		<u>Ex-smokers</u>	
	<u>Noranda</u>	<u>Michigan</u>	<u>Noranda</u>	<u>Michigan</u>	<u>Noranda</u>	<u>Michigan</u>
	<u>N=499</u>	<u>N=258</u>	<u>N=155</u>	<u>N=187</u>	<u>N=265</u>	<u>N=150</u>
	<u>Mean ± SD</u>	<u>Mean ± SD</u>	<u>Mean ± SD</u>	<u>Mean ± SD</u>	<u>Mean ± SD</u>	<u>Mean ± SD</u>
Age (years)	45.5 (14.1)	38.8 (12.8)	44.4 (14.1)	42.1 (17.7)	51.6 (13.8)	51.2 (15.2)
Height (in)	67.2 (2.9)	69.2 (2.7)	67.0 (2.6)	69.2 (2.7)	66.9 (2.3)	68.8 (2.6)
Lifetime packages of cigarettes	10.284	9.640	-	-	11.246	9.140
FVC (L)	4.48 (0.99)	4.86 (1.00)	4.68 (0.93)	4.97 (0.92)	4.28 (1.05)	4.59 (1.09)
FEV (L)	3.31 (0.92)	3.77 (0.90)	3.66 (0.73)	3.98 (0.79)	3.16 (0.99)	3.53 (0.96)
FEF _{50%} (L/sec)	3.82 (1.73)	4.27 (1.64)	4.77 (1.45)	4.73 (1.50)	3.88 (1.98)	4.15 (1.78)
FEF _{75%} (L/sec)	1.29 (0.81)	1.58 (0.80)	1.63 (0.73)	1.83 (0.77)	1.21 (0.77)	1.37 (0.72)
FEF _{25-75%} (L/sec)	2.77 (1.29)	3.37 (1.39)	3.39 (1.27)	3.80 (1.26)	2.95 (1.46)	3.14 (1.40)

* All smelter workers did not perform each test.

a greater cigarette consumption than those in Michigan. These findings are characteristic of industrial populations.

Mean spirometric values for the two populations are shown in Table 7-8.

The coefficients for the standard regression equations for each population (within the same smoking category) are shown in Table 7-9. They are similar. Thus, when values for smelter workers are adjusted to the age and height of the Michigan population, they are virtually identical for all smoking categories.

Figures 7-9 - 7-11 show the regression equations for the three spirometric measurements of the study and the comparison, non-smoker populations. The plots for FVC and FEV_1 are almost identical.

E. Prevalence of impairment

Table 10 shows the prevalence of spirometric impairment as conventionally defined for each test and smoking group among the active smelter workers and the Michigan control population. The prevalence of abnormal FVC is similar in the two populations when subjects in similar smoking categories are compared. The prevalences of abnormal FEV_1 and abnormal $FEF_{25-75\%}$ are slightly higher among smelter workers with a history of smoking. This may be in part related to their greater cigarette consumption. Most striking is a prevalence of 46% abnormal $FEF_{25-75\%}$ among non-smoking smelter workers, more than twice greater than that in the control population. These observations on prevalence confirm an effect of the smelter-exposure on a standard measurement of small airway function. Reduction in $FEF_{25-75\%}$ is not by itself evidence of disabling airway obstruction. Using a reduction in FEV_1 to a level $\leq 50\%$ of predicted as the criterion for clinical disability, only four workers would be so classified; all were current smokers.

Table 7 - 9

Standard regression coefficients for all Noranda employees and
for a comparison male general population (Michigan), by smoking category

	<u>Smokers</u>		<u>Ex-smokers</u>		<u>Non-smokers</u>	
	<u>Michigan</u>	<u>Noranda</u>	<u>Michigan</u>	<u>Noranda</u>	<u>Michigan</u>	<u>Noranda</u>
<u>FVC</u>	N = 218	N = 465	N = 120	N = 248	N = 153	N = 148
Height (in)	0.176	0.122	0.157	0.147	0.120	0.147
Age (years)	-0.037	-0.037	-0.040	-0.040	-0.030	-0.032
Constant	-5.980	-2.063	-4.145	-3.150	-2.120	-3.770
<u>FEV₁</u>	N = 218	N = 465	N = 120	N = 248	N = 153	N = 148
Height (in)	0.108	0.073	0.090	0.100	0.089	0.084
Age (years)	-0.042	-0.044	-0.040	-0.049	-0.030	-0.030
Constant	-2.070	0.350	-0.720	-1.037	-0.940	-0.664
<u>FEF_{25-75%}</u>	N = 218	N = 169	N = 120	N = 77	N = 153	N = 51
Height (in)	0.038	0.019	-0.030	0.060	0.074	0.042
Age (years)	-0.059	-0.062	-0.050	-0.049	-0.036	-0.044
Constant	3.040	4.150	5.970	1.090	0.150	2.480

Table 10

Prevalence of spirometric impairment
in active smelter workers

<u>FVC</u>	<u>N</u>	<u>SLIGHT 69.5 - 79.5 % predicted</u>	<u>MODERATE 49.5 - 69.5 % predicted</u>	<u>SEVERE < 49.5 % predicted</u>	<u>ALL IMPAIRED SUBJECTS</u>	<u>PREVALENCE IN CONTROL POPULATION</u>
Total	667	38 (5.70)	15 (2.40)	1 (0.15)	54 (8.25)	8.3
Smokers	375	29 (7.73)	11 (1.94)	1 (0.26)	41 (9.93)	10.4
Ex-smokers	172	8 (4.65)	3 (1.74)	0 (0)	11 (6.39)	10.0
Non-smokers	120	1 (0.83)	1 (0.83)	0 (0)	2 (1.66)	4.1
<u>FEV₁</u>						
Total	652	39 (5.98)	31 (4.75)	4 (0.64)	74(11.35)	6.3
Smokers	375	21 (5.60)	24 (6.40)	4 (1.06)	49(13.06)	9.1
Ex-smokers	172	15 (8.72)	7 (4.07)	0 (0)	22(12.79)	7.8
Non-smokers	105	3 (2.50)	0 (0)	0 (0)	3 (2.50)	1.0
<u>FEF_{25-75%}</u>		<u>59.5 - 74.5 % predicted</u>	<u>39.5 - 59.5 % predicted</u>	<u>< 39.5 % predicted</u>		
Total	259	52(20.01)	44(16.99)	23 (8.88)	119(45.95)	20.9
Smokers	148	26(17.57)	26(17.57)	18 (12.16)	70(47.30)	35.3
Ex-smokers	65	17(26.15)	14(21.54)	4 (6.15)	35(53.84)	42.5
Non-smokers	46	9(19.57)	4 (8.70)	1 (2.17)	14(30.44)	40.6

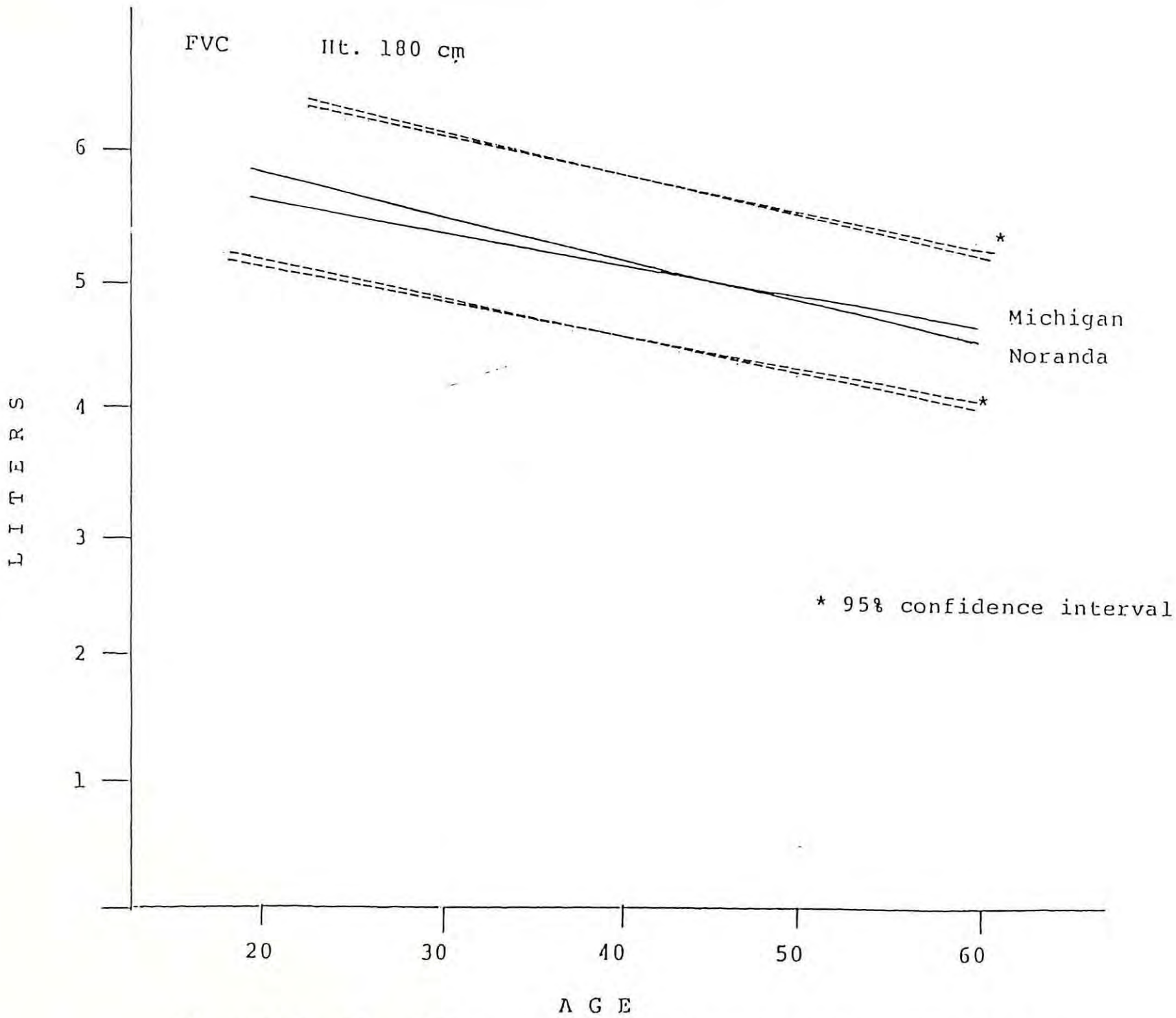


Figure 7-9: Plot of linear regression equation for FVC for non-smoking copper smelter employees (Noranda) and for non-smoking males in the comparison general population (Michigan).

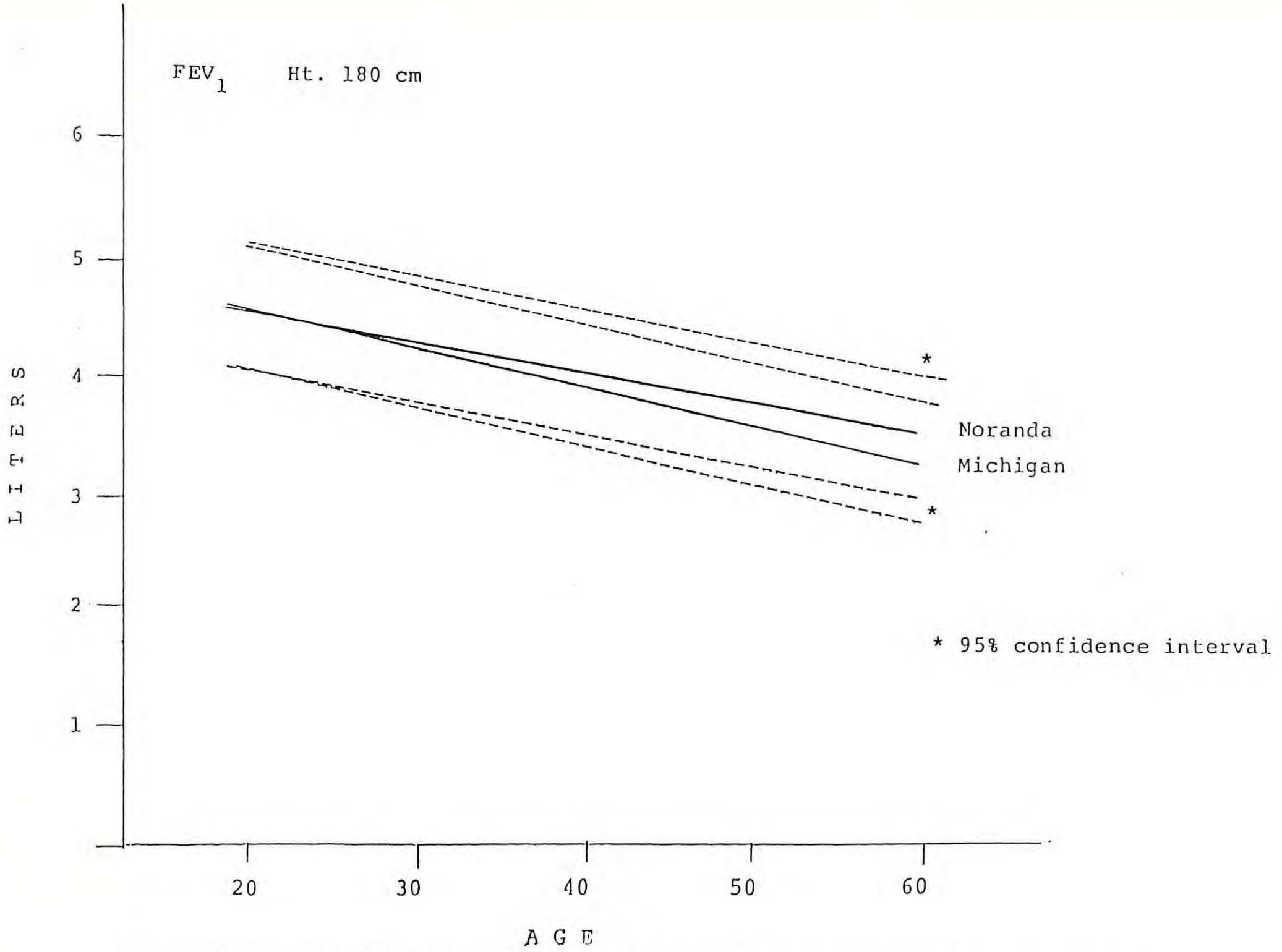


Figure 7-10: Plot of linear regression equation for FEV₁ for non-smoking copper smelter employees (Noranda) and for non-smoking males in the comparison general population (Michigan).

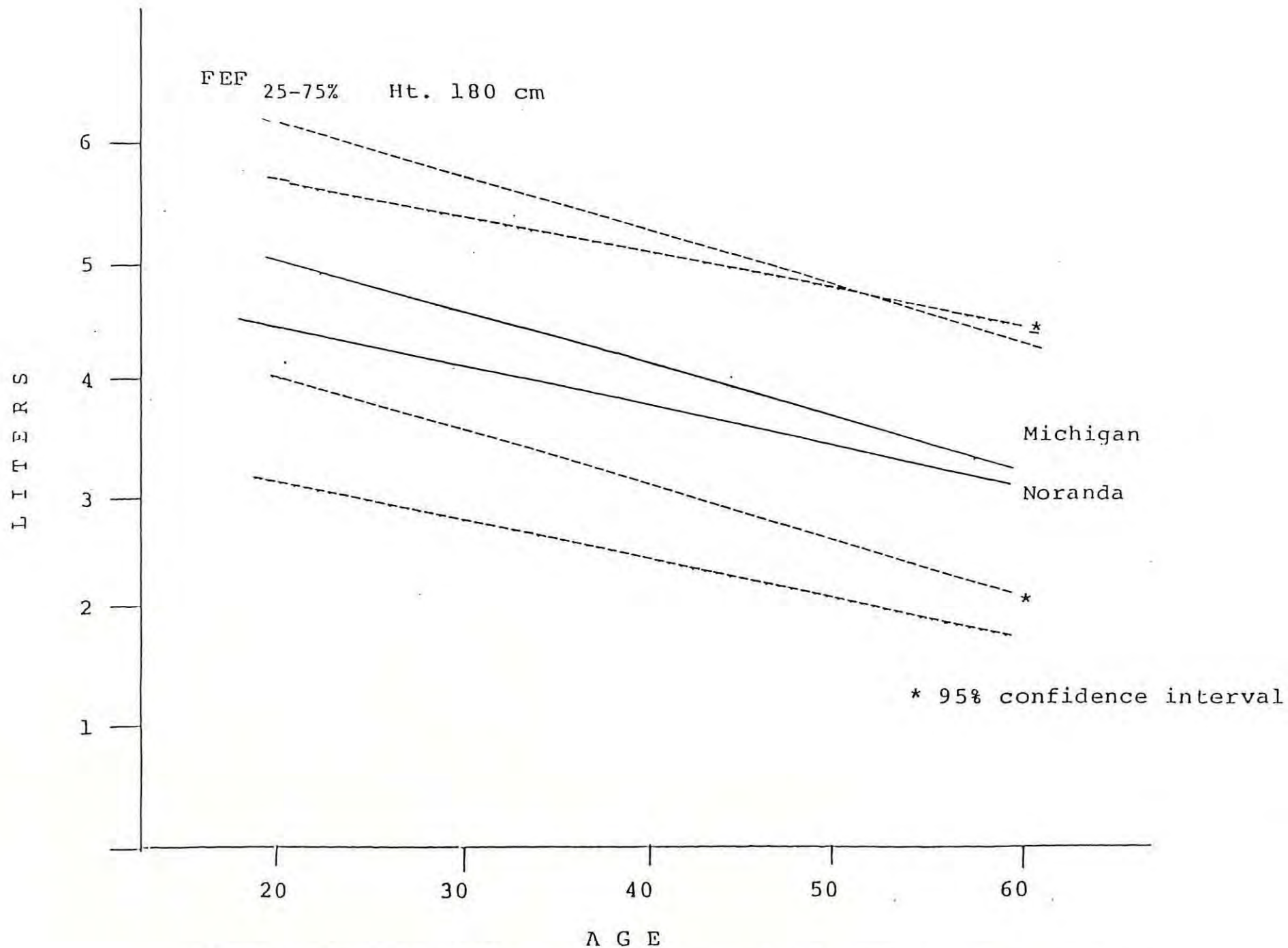


Figure 7-11: Plot of linear regression equation for $FEV_{25-75\%}$ for non-smoking copper smelter employees (Noranda) and for non-smoking males in the comparison general population (Michigan).

Summary

- 1) Comparing Noranda copper smelter workers and miners with white males in similar smoking categories drawn from the general population of the state of Michigan, there were no differences in three spirometric measurements (FVC, FEV₁, FEF_{25-75%}).
- 2) The strongest relationship between spirometric measurements in copper smelter workers (expressed as percent of the predicted reference value) was with urinary cadmium levels (Cd-U). The correlation between the two variables was greater than that between any spirometric measurement and age, height, pack-years of cigarette consumption, or years worked in the smelter.
- 3) Both smoking (pack-years) and occupational exposure (years in the smelter) contributed to the cadmium burden for the workers with a smoking history. Although the present study provides data on Cd-U in non-smoking, smelter-exposed subjects, there are no data on Cd-U in non-exposed subjects who smoke. Such data would allow better separation of the effects of smoking and smelter exposure on Cd-U and on lung function.
- 4) In non-smoking current smelter workers, whose cadmium body burden was obtained primarily from their employment, FEF_{25-75%} (a sensitive test of lung function) correlated with duration of employment and was lower in workers whose cadmium burden was greater. Prevalence of abnormal FEF_{25-75%} was more than twice greater in non-smoking smelter workers than in non-smoking controls from the general population.
- 5) Although the overall population of smelter employees did not differ from a comparison population, the correlations noted between pulmonary function and cadmium burden suggest that there is a subgroup with high cadmium burden in which pulmonary function is adversely affected. Such a subgroup would not be manifest in the overall population. This phenomenon is well known when evi-

dence of progressive chronic obstructive lung disease is sought in cigarette smokers, who are the overwhelming substrate for this disease.^{2 3} Looking at the mean values for all smokers masks the subgroup (approximately 10% of the total) who develop chronic progressive disease.

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Chapter VIII

Chest X-ray changes among copper smelter employees and miners

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All chest X-rays were reviewed at the examination site and subsequently at the Mount Sinai School of Medicine to determine if any serious disease, as cancer, was present on the radiograph. Individuals with suspicion of cancer or with other serious disease were immediately notified and referred for followup to the Department of Community Medicine at the Rouyn-Noranda Hospital. The radiographs were subsequently categorized using the ILO U/C International Classification of Pneumoconiosis (1971).¹ Each X-ray was interpreted independently by three experienced readers. Parenchymal changes of 1/0 were considered abnormal, as was the presence of pleural thickening, pleural plaques and/or pleural calcification. Additionally, other disease conditions were noted.

The results of the three readings were averaged, using the following criteria.

1. All parenchymal readings within a given category (rounded, irregular, and combined) were averaged, utilizing the ILO U/C 12 point scale [0/-=1, 0/0=2, etc.]).
2. If the range of individual readings exceeded three units, all readers reread that particular film with the indication that a disagreement existed in the parenchymal reading. In all cases, subsequent readings led to close agreement of the interpretations and the average of this second readings was utilized.
3. When disagreement existed among readers as to whether or not pleural changes existed, such films were also reread with the specification that a disagreement existed with respect to interpretation of the pleura. Following a second interpretation, a determination of abnormality was based upon the requirement that four of the six interpretations made consider the X-ray abnormal. A consensus of the individual readings determined the degree of abnormality.

Table 8-1 lists the number and percentage of X-ray abnormalities among the 831 mine and smelter employees who were invited to attend the examinations.

Overall, of those whose employment was only in the smelter, 14.9% of the X-rays were abnormal, 30.8% of those whose employment was only in mining were abnormal, and 21.9% of those whose employment included both mine and smelter work had abnormal X-rays. Among the abnormalities, 2 of 353 (0.5%) X-rays of smelter workers showed small rounded opacities. In contrast, 5 of 54 (6.4%) of those employed only in mining had such abnormalities, 11 of 264 (3.3%) mine and smelter workers had small rounded opacities. This presumably follows from the greater opportunity for exposure to silica dust in mining activities. Small, irregular opacities were commonly seen in all employment groups, 9.6% among smelter workers, 16.7% among miners and 11.5% among those with combined employment. Pleural abnormalities, too, were often evident, 7.5% in smelter workers, 15.4% in miners, and 11.5% in those with both mine and smelter work. This prevalence would indicate past exposure to dusts other than silica, including asbestos. In general, the degree of abnormality was of the lowest major ILO U/C category. Only 2 individuals had a profusion of small opacities of grade 2/1 or greater.

However, as previously indicated, the employment distribution of the individuals working in the smelter differed considerably from those with mining activity; the smelter workers generally being younger and more recently employed. Thus, overall comparisons between the groups can be misleading because of the significantly different work histories. Therefore, a standardized percentage of X-ray abnormalities was estimated; this calculates percentage of abnormalities that would be present if all groups under consideration had the same distribution of duration of exposure or time from onset of exposure. It is calculated as follows:

$$\% \text{ Std} = \frac{N \text{ int}}{N \text{ tot}} \% \text{ int}$$

where: % Std = standardized percentage

% int = percentage abnormal in a category interval
(a 10 year interval, e.g.)

N int = Number of individuals in interval

N tot = Total number of individuals
(in all intervals)

Table 8 - 1

Chest X-ray abnormalities
among 831 mine and smelter employees

X-ray reading	<u>Smelter</u>		<u>Mine</u>		<u>Both mine & smelter</u>	
	Num.	%	Num.	%	Num.	%
Normal X-ray	353	85.1	54	69.2	264	78.1
Parenchymal abnormalities	42	10.1	15	19.2	46	13.6
Small rounded opacities	2	0.5	5	6.4	11	3.3
1/0 - 1/2	2	0.5	4	5.1	11	3.3
2/1 - 2/3	0	0.0	1	1.3	0	0.0
Small irregular opacities	40	9.6	13	16.7	39	11.5
1/0 - 1/2	39	9.4	13	16.7	39	11.5
2/1 - 2/3	1	0.2	0	0.0	0	0.0
Parenchymal abnormalities only	32	7.7	12	15.4	35	10.4
Pleural abnormalities	31	7.5	12	15.4	39	11.5
Pleural fibrosis	22	5.3	12	15.4	33	9.8
Pleural calcification	2	0.5	0	0.0	4	1.2
Diaphragmatic plaque(s)	9	1.9	0	0.0	9	2.2
Pleural abnormalities only	21	5.1	9	11.5	28	8.3
Parenchymal and/or pleural abnormalities	<u>62</u>	14.9	<u>24</u>	30.8	<u>74</u>	21.9
Total X-rays	415		78		338	

Tables 8-2 and 8-3 list the numbers and percentages of abnormal X-rays according to years from onset of employment and total years of employment in the smelter or in a mine. In each case, standardized percentages of X-ray abnormalities are calculated based upon the distribution of years from onset of employment and total years of employment of the entire group of invitees. The standardized percentages of abnormalities, with the exception of the small rounded opacities, are very similar across the three work activities. Overall, the percentage of individuals with any X-ray abnormality, standardized to years from onset of exposure, is 21.8% among smelter workers, 19.4% among miners, and 17.4% among those with both mine and smelter employment. Parenthetically, the group of 101 individuals who appeared for examination on their own volition and whose employment was largely in mining, had virtually the identical standardized percentages of abnormalities as those miners who were invited for examination.

The number and percentage of abnormal X-rays according to the seven major work activity categories is listed in Table 8-4. As can be seen, the standardized percentage is quite similar for four of the seven principal groups, with general maintenance workers perhaps having a higher percentage of abnormalities than the other groups. Workers employed in the casting of copper and those in the plate, machine, and electrical shops had significantly fewer abnormalities than those with more general smelter exposure, or exposure to the high concentration of dusts in the reactor areas. An age-standardized percentage of X-ray abnormalities according to years from onset of employment was calculated for all invited workers, and for those whose employment consisted only of smelter work (Table 8-5). The age-standardized percentage of abnormalities for individuals employed less than 30 years from onset of employment was less than those whose employment began 30 or more years previously. However, because of the relatively small number of individuals with abnormal X-rays in a given exposure category, the differences did not achieve statistical significance at the 5% level.

Comparison of the abnormal X-rays with pulmonary function test results shows a strong correlation of X-ray abnormality with pulmonary function deficit. Table 8-6 lists the means of the four principal pulmonary func-

Table 8 - 2

The distribution of X-ray abnormalities according to
years from onset of employment among
831 mine and smelter employees

Years from onset of employment	<u>E m p l o y m e n t</u>					
	<u>Smelter</u>		<u>Mine</u>		<u>Both mine & smelter</u>	
	Num.	%	Num.	%	Num.	%
	<u>Small rounded opacities</u>					
0 - 9	1/138	0.7	0/4	0.0	0/23	0.0
10 - 19	0/130	0.0	0/5	0.0	0/56	0.0
20 - 29	0/93	0.0	1/13	7.7	1/92	1.1
30 - 39	1/43	2.3	2/35	5.7	9/136	6.6
40+	0/11	0.0	2/21	9.5	1/31	3.2
Standardized percentage	0.7 ± 0.6		4.1 ± 2.2		2.2 ± 0.7	
	<u>Small irregular opacities</u>					
0 - 9	2/138	1.4	0/4	0.0	1/23	4.4
10 - 19	13/130	10.0	0/5	0.0	1/56	1.8
20 - 29	11/93	11.8	3/13	23.1	8/92	8.7
30 - 39	10/43	23.3	6/35	17.1	23/136	16.9
40+	4/11	36.4	4/21	19.0	6/31	19.4
Standardized percentage	14.2 ± 2.6		11.4 ± 3.7		9.2 ± 1.6	
	<u>Combined profusion</u>					
0 - 9	3/138	2.2	0/4	0.0	1/23	4.4
10 - 19	13/130	10.0	0/5	0.0	1/56	1.8
20 - 29	12/93	11.8	4/13	30.8	9/92	9.8
30 - 39	10/43	23.3	6/35	17.1	28/136	20.6
40+	4/11	36.4	5/21	19.0	7/31	22.6
Standardized percentage	14.3 ± 2.6		13.2 ± 4.1		10.6 ± 1.7	

(continued)

Table 8 - 2 (continued)

Years from onset of employment	<u>E m p l o y m e n t</u>					
	<u>Smelter</u>		<u>Mine</u>		<u>Both mine & smelter</u>	
	Num.	%	Num.	%	Num.	%
	<u>Pleural abnormalities</u>					
0 - 9	4/138	2.9	0/4	0.0	0/23	0.0
10 - 19	10/130	7.7	0/5	0.0	3/56	5.4
20 - 29	6/93	6.5	1/13	7.7	8/92	8.7
30 - 39	9/43	20.9	7/35	20.0	18/136	13.2
40+	3/11	27.3	4/21	19.0	10/31	32.3
Standardized percentage	11.4 ±	2.3	8.4 ±	2.8	9.2 ±	1.5
	<u>Any X-ray abnormality</u>					
0 - 9	5/138	3.6	0/4	0.0	1/23	4.4
10 - 19	19/130	14.6	0/5	0.0	4/56	7.1
20 - 29	16/93	17.2	4/13	30.8	14/92	15.2
30 - 39	17/43	39.5	13/35	37.1	40/136	29.4
40 +	5/11	45.5	7/21	33.3	15/31	48.4
Standardized percentage	21.8 ±	3.2	19.4 ±	4.6	17.4 ±	2.2

Table 8 - 3

The distribution of X-ray abnormalities according to
total years of employment among
831 mine and smelter employees

Total years of employment	<u>Employment</u>					
	<u>Smelter</u>		<u>Mine</u>		<u>Both mine & smelter</u>	
	Num.	%	Num.	%	Num.	%
	<u>Small rounded opacities</u>					
0 - 9	1/140	0.7	0/4	0.0	0/37	0.0
10 - 19	0/140	0.0	0/9	0.0	0/65	0.0
20 - 29	0/91	0.0	1/28	3.6	2/97	2.1
30 - 39	1/38	2.6	4/33	12.1	9/129	7.0
40 +	0/6	0.0	0/4	0.0	0/10	0.0
Standardized percentage	0.8 ± 0.6		3.8 ± 1.7		2.2 ± 0.7	
	<u>Small irregular opacities</u>					
0 - 9	3/140	2.1	0/4	0.0	1/37	2.7
10 - 19	15/140	10.7	1/9	11.1	0/65	0.0
20 - 29	12/91	13.2	3/28	10.7	16/97	16.5
30 - 39	8/38	21.1	8/33	24.2	17/129	13.2
40+	2/6	33.3	1/4	25.0	5/10	50.0
Standardized percentage	12.1 ± 2.3		12.1 ± 3.9		9.3 ± 1.5	
	<u>Combined profusion</u>					
0 - 9	4/140	2.9	0/4	0.0	1/37	2.7
10 - 19	15/140	10.7	1/9	11.1	0/65	0.0
20 - 29	13/91	14.3	4/28	14.3	18/97	18.6
30 - 39	8/38	21.1	9/33	27.3	22/129	17.1
40+	2/6	33.3	1/4	25.0	5/10	50.0
Standardized percentage	12.3 ± 2.2		13.8 ± 4.2		10.7 ± 1.6	

Table 8 - 3 (continued)

Total years of employment	<u>Employment</u>					
	<u>Smelter</u>		<u>Mine</u>		<u>Both mine & smelter</u>	
	Num.	%	Num.	%	Num.	%
	<u>Pleural abnormalities</u>					
0 - 9	4/140	2.9	0/4	0.0	1/37	2.7
10 - 19	11/140	7.9	0/9	0.0	3/65	4.6
20 - 29	6/91	6.6	4/28	14.3	11/97	11.3
30 - 39	9/38	23.7	7/33	21.2	22/129	17.1
40+	1/6	16.7	1/4	25.0	2/10	20.0
Standardized percentage	10.5 ±	2.2	9.4 ±	2.7	9.3 ±	1.6
	<u>Any X-ray abnormality</u>					
0 - 9	6/140	4.3	0/4	0.0	2/37	5.4
10 - 19	22/140	15.7	1/9	11.1	3/65	4.6
20 - 29	16/91	17.6	7/28	25.0	24/97	24.7
30 - 39	16/38	42.1	15/33	45.5	39/129	30.2
40+	2/6	33.3	1/4	25.0	6/10	60.0
Standardized percentage	20.5 ±	3.0	20.9 ±	4.8	17.5 ±	2.1

Table 8 - 4

Chest X-ray abnormalities
according to work activity

Work activity	Normal X-rays	Abnormal X-rays	Percentage abnormal	Standardized ¹ percentage of abnormal
Crusher and concentrator	27	4	12.9	24.3
Reactor/furnace	101	17	14.4	20.5
Converter	36	7	16.2	22.8
Anodes	21	0	0.0	0.0
Inside shops	35	3	7.9	9.3
Maintenance	56	16	22.2	29.7
Other smelter	77	15	16.3	23.4
Total	357	62	14.9	21.8

¹ Standardized to the distribution of years from onset of all invited participants in the survey; 0-9, 19.9%; 10-19, 23.0%; 20-29, 23.8%; 30-39, 25.8%; 40+, 7.6%.

Table 8 - 5

Age standardized
percentage of X-ray abnormalities
in mine and smelter workers according
to time from onset of employment

Group	<u>Years from onset of employment</u>	
	<u>Less than 30</u>	<u>30 or more</u>
Invited mine and smelter workers (1)	20.9 ± 3.6	28.4 ± 4.5
Invited smelter workers (2)	21.4 ± 5.8	34.7 ± 6.1

1) Standardized using data for those aged 40 - 69

2) Standardized using data for those aged 50 - 69

Table 8 - 6

Smoking standardized pulmonary function
parameters according to X-ray reading

Pulmonary function parameters	X-ray reading	
	Normal	Abnormal
<u>Miners</u>		
FVC/PFVC	94.7 ± 2.5	84.0 ± 5.4
FEV ₁ /PFEV ₁	95.4 ± 2.9	83.2 ± 7.8
FEV ₁ /FVC	71.9 ± 1.4	66.9 ± 3.8
MMF/PMMF	69.6 ± 11.3	Insuf. data
<u>Smelter Workers</u>		
FVC/PFVC	99.0 ± 0.8	93.6 ± 2.3
FEV ₁ /PFEV ₁	100.0 ± 0.9	92.3 ± 2.9
FEV ₁ /FVC	76.4 ± 0.5	71.0 ± 1.2
MMF/PMMF	80.3 ± 2.8	67.3 ± 4.5
<u>Mine and Smelter Workers</u>		
FVC/PFVC	97.9 ± 1.0	91.7 ± 2.2
FEV ₁ /PFEV ₁	99.9 ± 1.2	91.2 ± 2.6
FEV ₁ /FVC	74.8 ± 0.7	69.8 ± 1.3
MMF/PMMF	80.5 ± 3.1	74.6 ± 9.6

PFVC = Predicted FVC
PFEV₁ = Predicted FEV₁
PMMF = Predicted MMF

tion parameters according to work activity and X-ray reading. In this comparison, smoking standardized pulmonary function values were used, which removes the confounding effect of cigarette smoking.

Overall, miners had greater pulmonary function deficits than smelter workers and those miners with abnormal X-rays had the greatest deficits of all. The means of the various pulmonary function tests among miners with abnormal X-rays was 5 - 12 percentage points lower than among those with normal X-rays. Similarly, among smelter workers, a 5 - 13 percentage decrease in pulmonary function test results was seen among those with abnormal X-rays.

The spirometry of individuals with mine and smelting employment was somewhat similar to the smelter workers and also reflected significant deficits associated with abnormal X-rays.

Summary of X-ray findings

Onset and employment standardized percentages of X-ray abnormalities for 831 mine and smelter employees ranged from 17.4% to 21.8%. A slightly greater percentage of small irregular opacities was seen in smelter workers than in miners or men with combined employment. Small rounded opacities were confined largely to those with mining experience. Among smelter workers, those in maintenance were most affected and those in the casting line or inside shops (electricians, carpenters, painters, etc.) the least. Further, the age standardized percentage of X-ray abnormalities correlated strongly with time from onset of exposure and the overall X-ray abnormalities with deficits in observed spirometric parameters.

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CHAPTER IX

Lung cancer in copper smelter employees

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Occupational exposure in copper smelters has been shown to be associated with an increased risk of respiratory cancer, in a number of epidemiologic studies;^{1 6} in most of these the etiologic agent considered responsible has been thought to be inorganic arsenic.

While the magnitude of the excess risk for respiratory cancer in copper smelters has varied in different studies, it is noteworthy that in a Japanese cohort study an almost 12-fold increase in the number of deaths from cancer of the trachea, bronchus and lung was found. Excess respiratory cancer was present in all smoking categories (in those studies in which smoking status was assessed).⁷

A number of epidemiologic studies have also documented increased respiratory cancer mortality in areas where environmental contamination due to emissions from copper smelters had been documented.^{8 9 10}

The recently completed mortality study on the Rouyn-Noranda region¹¹ has reported that an excess mortality from lung cancer exists in the Rouyn-Noranda population, when compared to that in two other locations.

The cross-sectional medical examination of Noranda copper smelter employees and miners did not attempt to assess the problem of excessive respiratory cancer risk in this population; such evaluation can only be expected from carefully conducted epidemiological studies. A number of cases of lung cancer were, nevertheless, detected during the medical examination; chest X-ray films were reviewed on site and in all cases of suspicious radiologic opacities an attempt was made to compare findings with those on pre-existing chest X-ray films. Dr. Real Lacombe was of great help in providing, whenever possible, prior chest X-ray films. After thorough consideration of these cases, a list was prepared, including all persons for whom further clinical work-up and/or radiologic follow-up was recommended, to rule out lung cancer. Again, Dr. Lacombe took responsibility for this follow-up. This led to the detection of 5 cases of lung cancer during, or immediately after the clinical examinations.

With regard to the 5 cases of lung cancer found and confirmed during or immediately after the clinical examination, the relevant characteristics were:

<u>Age</u>	<u>Occupation</u>	<u>Smoking status</u>	<u>As-U/ g creatinine</u>	<u>Cd-U/ g creatinine</u>	<u>Other chest X-ray changes</u>
66	miner	smoker	3 µg	1.8 µg	s 1/1
55	miner	ex-smoker	8 µg	3.0 µg	p 0/1
46	miner	ex-smoker	22 µg	1.8 µg	s 0/1
72	miner	smoker	-	-	0/0
55	active smelter worker	smoker	24 µg	0.6 µg	t 1/0

The miners had spent between 18 (in two cases) and 35 years underground; the active smelter employee had initially worked for 25 years in the mine, and had taken on work in the smelter 3 years prior to the examination.

It has been the experience of our laboratory and that of other investigators that the presence of previously undiagnosed lung cancer in cross-sectional clinical surveys of employed workers is uncommon, unless carcinogenic agents are present, and the finding of five such cases among 920 examined is of considerable concern.

This conclusion has been strengthened by the fact that since the conclusion of the clinical examination, information has been forwarded to the Environmental Sciences Laboratory, indicating that another 4 cases of lung cancer had been diagnosed and are either deceased or have undergone surgery.

The relevant characteristics of these cases are:

<u>Age</u>	<u>Occupation</u>	<u>Smoking status</u>	<u>As-U/ g creatinine</u>	<u>Cd-U/ g creatinine</u>	<u>Other chest X-ray changes</u>
46	active smelter worker	ex-smoker	6	0.9	0/0
62	active smelter worker	smoker	6	3.8	0/0
62	miner	smoker	10	1.2	s/q 0/1; right pl. fibrosis
51	miner	ex-smoker	33	1.9	t 1/0

The detection of at least nine cases of lung cancer among those examined, some during the cross-sectional medical examination and others in the period between the examination and the completion of this report, is consistent with an excess lung cancer risk in copper smelter workers, repeatedly reported in the literature for other copper smelter facilities.

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Chapter X

Summary of Major Findings and Conclusions

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Lead, cadmium and arsenic emissions from a large copper smelter were found to result in environmental contamination in the nearby community. With the information on environmental contamination documenting undue exposure to the population living around the smelter, the need for a comprehensive assessment of the health status of workers in the copper smelter was recognized.

A medical examination of 920 men was undertaken: 680 were active smelter workers, and 96 retired smelter employees (some of whom had also worked in the mine); 144 men who had never worked in the smelter itself, but who had worked as copper or/and gold miners in the area were also included.

A summary of the scientific report follows. (Each examined worker has already received a personal medical report).

We have carefully considered conditions and/or factors that may either hide significant medical findings or falsely suggest positive results. These are pointed in the full report (Chapters I - IX).

A. Lead Exposure.

In general, actively employed smelter workers had higher blood lead levels than retirees and miners; 17% of smelters had levels exceeding 40 micrograms per 100 milliliters of blood, the upper acceptable limit in most countries. However, only a very small proportion of smelter employees (less than 1%) had blood lead levels exceeding 60 micrograms per 100 milliliters of blood, a level considered hazardous.

On the average, riggers, reactor feeders and dust collectors had the highest blood lead and zinc protoporphyrin levels. Zinc protoporphyrin is a sensitive indicator of lead absorption and subsequent effects on blood constituents. However, elevated values of blood lead and zinc protoporphyrin were also found in other job categories. Detailed tables in Chapter II should be examined for this particular aspect.

When comparing active copper smelter employees with miners, no major differences were found in reported prevalence of symptoms suggestive of adverse lead-induced effects. Sleep disturbances, fatigue, joint pain, tingling sensations in the extremities, and muscle pain were the most frequent symptoms reported by active copper smelter employees. Joint pain was the most frequent symptom in miners.

When comparing the prevalence of these symptoms among smelter workers with the same symptoms among a group of autobody shop employees exposed to lead only, no significant differences in prevalence of symptoms were found. Sleep disturbances, weight loss and muscle pain were the only symptoms with slightly higher prevalence among copper smelter workers; other toxic exposures - such as arsenic and cadmium - may explain the relatively higher prevalence of symptoms.

None of the workers had clinical evidence (on physical examination for neurologic deficit) compatible with a clinical picture of toxic peripheral neuropathy, such as seen with toxic lead exposure.

Special behavioral and electrophysiologic tests were administered to determine whether the relatively low lead levels posed any health problem among copper smelter workers.

We did not find that lead exposure in the copper smelter was associated with a decrement of brain function, as measured by a limited battery of neurobehavioral/mental tests. The same battery of tests has been used to study workers exposed to higher levels of lead in other industries (secondary lead smelters). There, deterioration of mental function among workers exposed to higher levels of lead absorption has been well documented.

One test raised some questions of neurophysiological lead effects. While lead exposure was not associated with disruption of normal patterns of eye movements, (disruption in these patterns is a sensitive indicator of nervous system dysfunction) in some measures of eye movements there were significant differences between copper smelter em-

ployees and control, non-exposed persons. It is possible that these measures of eye movements could be more sensitive than other parameters of neurological function in the detection of early neurotoxic effects of lead.

A slight decrease (limited) in the speed with which nervous impulses are transmitted along the nerves in the limbs ("nerve conduction velocity") was also found. However, the possibility that this abnormality might be the effect of multiple exposures (lead and arsenic) has to be considered, and we cannot conclude that it was due to lead alone.

In summary, while blood lead and zinc protoporphyrin levels were significantly elevated in active copper smelter employees, indicating occupational exposure and absorption of lead, the levels were relatively low when compared to other occupational groups with lead exposure.

Major differences with regard to symptoms or findings on physical examination were not found. With more sensitive methods, slight changes in the normal pattern of eye movements and in the speed with which nervous impulses are transmitted along the nerves in the limbs were found. For some of these changes, the simultaneous exposure to other toxic substances, such as arsenic, might have contributed.

B. Cadmium Exposure.

In general, blood cadmium reflects recent exposure and as a result is a relatively unstable measure since it would vary with changing conditions. Urinary cadmium, on the other hand, reflects long-term exposure and is therefore a more stable measure than blood cadmium. Because both measures are needed for an accurate assessment of cadmium absorption, cadmium levels were measured in blood and urine.

Blood cadmium levels were significantly higher among smelter employees than in miners. Slightly elevated levels of blood cadmium were also observed among retirees and miners. This may reflect environmental cadmium contamination in the vicinity of the smelter.

Urinary cadmium levels were significantly higher among retirees than among active smelter employees. Relatively older age may be one factor since urinary cadmium is known to increase with age. Longer exposure in the smelter and higher accumulation of cadmium in the body is most probably the more important factor. Urinary levels of cadmium did not exceed 10 micrograms/g creatinine in any of the workers. This level is considered to be the critical level for kidney impairment.

The report includes job categories ranked by increasing levels of blood and urinary cadmium. Detailed tables in Chapter II should be examined. Briefly, workers with the highest median blood cadmium levels (4 micrograms/liter or more) were employed at the following jobs: power house boiler, dust collector, reactor feeder, concentrator-unloading shed, and roaster or mixing.

Workers who had elevated blood cadmium and elevated urinary cadmium also had elevated blood lead levels. This indicates that exposure to lead and cadmium has a common source in the impurities of copper concentrates.

It was found that blood cadmium and urinary cadmium levels were a function of exposure to fumes and dusts containing cadmium, as well as cigarette smoking. Smoking was found to considerably increase cadmium absorption.

The relationship between cadmium and radiologic indicators of emphysema was explored. Urinary cadmium was found to be one of the important factors associated with emphysema. Other factors were age, smoking and length of employment at the smelter.

Urinary cadmium was also found to be one of the leading factors associated with a decrease in lung function as determined by special tests of respiratory function. Other factors contributed as well - particularly cigarette smoking.

An association between urinary cadmium and elevated blood pressure was observed in active workers and retirees; no such correlations were observed among miners.

The effects of cadmium on kidney function were less evident among copper smelter employees than other cadmium-exposed groups reported in the medical literature, with higher levels of cadmium absorption and urinary cadmium excretion.

In this study, cadmium seemed to influence the body's ability to process calcium and phosphorous. This was particularly true among copper smelter workers. These biological effects of cadmium have been reported in the medical literature.

In summary, while there was evidence of undue cadmium absorption and while some effects were seen, these did not reach proportions which have been elsewhere discovered to have immediate, serious consequences.

C. Arsenic Exposure.

Significantly higher levels of urinary arsenic were present in active smelter workers.

Workers who had elevated urinary arsenic levels were also likely to have elevated blood lead levels. Urinary arsenic did not exceed 0.2 milligrams per liter in any of the job categories, except for reactor feeders.

As explained above, arsenic absorption may be a co-factor (particularly with lead) in the reduction of nerve conduction velocities.

Effects of lead, cadmium and arsenic in the population studied are general trends observed in a large number of workers. When stratifying according to mean levels of lead, arsenic and cadmium in

job categories, it becomes obvious that higher exposures are characteristic for some of the job categories. To prevent adverse health effects due to toxic exposure in the copper smelter, particular efforts should be directed towards reducing levels of exposure in the job categories found to rank highest. Medical surveillance and monitoring should also give priority to those at highest risk.

Because of the well known carcinogenic effects of arsenic, examination of the skin was given special attention (potential for arsenic-induced skin changes including cancer); this did not reveal significant findings. Skin cancer had occurred, but with the prevalence expected in the general population.

Although a cross-sectional clinical examination cannot provide complete answers with regard to carcinogenic effects of occupational health hazards (these have to rely on long-term epidemiologic studies), the finding of previously undiagnosed lung cancer cases during cross-sectional clinical surveys of employed workers is uncommon, and is a reason for serious concern. The finding of five lung cancer cases and 3 highly suspicious cases among 920 examined copper smelter employees and miners during the examination is consistent with an excess lung cancer risk in copper smelter workers and in areas around copper smelters, repeatedly reported in the literature, and also found for the Rouyn-Noranda area. The most probable etiologic factor is arsenic exposure, although other factors (SO_2 , mineral fibers) cannot be excluded.

In the time period between the completion of the examination and the conclusion of this report another 11 cases were suspected of lung cancer; four of these were confirmed. The number of lung cancer cases in the examined population of copper smelter employees and miners points to the presence of at least one carcinogen in the work environment. Arsenic exposure should be given special attention and engineering controls to reduce this exposure should receive high priority.

Since smoking is an important factor in lung cancer and can, due to multiple factor interaction, increase the effects of occupational carcinogens, a sustained educational anti-smoking program for the copper smelter employees would be of major importance.

D. Chest X-ray changes.

Radiologic changes consisting in irregular opacities and small rounded opacities were detected on chest X-ray films of a proportion of those examined. Usually such changes are associated with the effect of inhaled inorganic dusts on the lung (pneumoconioses). In the smelter environment, inorganic dust is present, although other exposures, such as gases (SO_2) or fumes (cadmium), could also contribute to the pulmonary effects detected on chest X-ray and through pulmonary function tests.

Prevalence of chest X-ray abnormalities for 831 smelter and mine employees ranged from 17.4% to 21.8%. Small rounded opacities were confined largely to those with mining experience and most probably represent the effect of silica exposure. Small irregular opacities were found with a slightly higher prevalence in smelter workers than in miners or men with combined employment. Among smelter workers, those in maintenance were most affected and those in the casting line or inside shops (electricians, carpenter, painters, etc.) the least. Further, the age-standardized percentage of X-ray abnormalities correlated strongly with time from onset of exposure, and the overall X-ray abnormalities with deficits in observed spirometric parameters.

E. Pulmonary function tests.

Pulmonary function tests (PFTs), including spirometry and flow rates at low lung volumes, reveal effects of exposures which may not be seen on clinical examination or chest X-ray. This is particularly true for effects on the airways. Three measurements of pulmonary function were used:

FVC - to detect scarring of the lungs (fibrosis)

FEV₁ and its relationship to FVC - to detect obstructive
bronchitis

FEF_{25-75%} - to detect changes in the small airways
(dust deposition, bronchiolitis)

A strong relationship was found between PFTs and overall cadmium exposure (cadmium body burden expressed as urinary cadmium). Cadmium body burden originates in smelter exposure and cigarette smoking. The relative effects of each factor are difficult to separate in smoking smelter workers.

Evidence for the effect of occupational exposure was seen in the most sensitive test, the FEF_{25-75%} when it was applied to non-smokers. This measurement was inversely correlated with duration of employment. It was reduced in a larger percentage of these workers than of the general population. A change in pulmonary function of this nature is not disabling, although it may presage progressive disease. No other differences in pulmonary function were found in comparison with the general population. It is not possible to say which material in the smelter environment (e.g. SO₂, cadmium, other dusts) caused this change in pulmonary function.