NIOSH

CRITERIA FOR A RECOMMENDED STANDARD.... OCCUPATIONAL EXPOSURE TO

INORGANIC LEAD

Revised Criteria - 1978

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

criteria for a recommended standard....

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PREFACE TO THE REVISED RECOMMENDED STANDARD

The original criteria document for an Occupational Exposure to Inorganic Lead was published January 5, 1973.

On January 15, 1976, the Occupational Safety and Health Administration published a proposal for a revised occupational health standard for inorganic lead. At the same time NIOSH initiated an evaluation of the scientific literature published since the original document was issued. The Occupational Safety and Health Administration held hearings during the period of July 1-15, 1977, at which NIOSH presented testimony. This revised criteria document is based on the new information gained from the literature evaluation and reflects the NIOSH testimony which is included as Appendix V.

The primary changes in the recommended standard are a lowering of the permissible exposure level from 150 to 100 $\mu g/m^3$, lowering of the maximum blood level from 80 to 60 $\mu g/100$ g, revised recommendations for respiratory protection, and more up-to-date recommendations regarding work practices and sanitation.

New information on biologic effects, sampling and analysis, and work practices and sanitation are included in Appendix IV.

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Assistant Surgeon General
Acting Director, National Institute
for Occupational Safety and Health

The Office of Research and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for development of the criteria and recommended standard for inorganic lead. Keith H. Jacobson, Ph.D., had program responsibility and Robert E. Seiter served as criteria manager. Frank W. Mackison had program responsibility for preparation of the revised recommended standard for inorganic lead.

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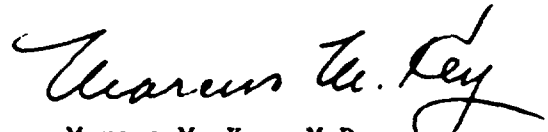
PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards at their workplace. To provide relevant data from which valid criteria and effective standards can be deduced, the National Institute for Occupational Safety and Health has projected a formal system of research, with priorities determined on the basis of specified indices.

It is intended to present successive reports as research and epidemiologic studies are completed and sampling and analytical methods are developed. Criteria and standards will be reviewed periodically to ensure continuing protection of the worker.

I am pleased to acknowledge the contributions to this report on inorganic lead by my staff and the valuable constructive comments by the Review Consultants on Inorganic Lead, by the ad hoc committee of the American Academy of Industrial Hygiene, by Robert P. O'Connor, M. D., NIOSH consultant in occupational medicine, and Edwin C. Hyatt on respiratory protection. The NIOSH recommendations for standards are not necessarily a consensus of all of the consultants and professional societies that reviewed this criteria document on inorganic lead. A list of the NIOSH Review Committee members and of the Review Consultants appears on pages iii and iv.[revised pages vii and viii].



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CRITERIA DOCUMENT: REVISED RECOMMENDATIONS FOR AN OCCUPATIONAL EXPOSURE STANDARD FOR INORGANIC LEAD

CONTENTS

I. REVISED RECOMMENDATION FOR AN INORGANIC LEAD STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that employee exposure to inorganic lead in the workplace be controlled by adherence to the following sections. The standard is designed to protect the health and safety of workers for a 10-hour day, 40-hour week over a working lifetime; compliance with the standard should therefore prevent adverse effects of lead on the health and safety of workers. The standard is measurable by techniques that are valid, reproducible, and available to industry and government agencies. Sufficient technology exists to permit compliance with the recommended standard. The criteria and standard will be subject to review and revision as necessary.

"Inorganic lead" means lead oxides, metallic lead, and lead salts (including organic salts such as lead soaps but excluding lead arsenate). "Exposure to inorganic lead" is defined as exposure above half the recommended workroom environmental standard. Exposures at lower environmental concentrations will not require adherence to the following sections, except for Section 7(a).

Section 1 - Environmental (workplace air) - (see NIOSH testimony Appendix V - page XII-1)

(a) Concentration

Occupational exposure to inorganic lead shall be controlled so that workers shall not be exposed to inorganic lead at a concentration greater than 0.10 mg Pb/m^3 determined as a time-weighted average (TWA) exposure for an 10-hour workday, 40-hour work week.

(b) Sampling and Analysis

Procedures for collection of environmental samples shall be as provided in Appendix I, or by an equivalent method. Analysis of samples shall be as provided in Appendix II, or by any method shown to be equivalent in precision and accuracy to the method specified in Appendix II.

Section 2 - Medical - (see NIOSH testimony Appendix V - page XII-1)

Medical monitoring (biologic monitoring and medical examinations) shall be made available to workers as outlined below.

(a) Biologic monitoring

Biologic monitoring shall be made available to all workers subject to "exposure to inorganic lead." This consists of sampling and analysis of whole blood for lead content. Such monitoring shall be performed to ensure that no worker absorbs an unacceptable amount of lead. Unacceptable absorption of lead posing a risk of lead poisoning is demonstrated at levels of 0.060 mg Pb/100 g of whole blood or greater.

Procedures for sampling and analysis of blood for lead shall be as described in Appendix II, or by any method shown to be equivalent in precision and accuracy.

All workers subject to "exposure to inorganic lead" shall be offered biologic monitoring at least every 6 months. The schedule of biologic monitoring may be made more frequent if indicated by a professional industrial hygiene survey. If environmental sampling and analysis show that environmental levels are at or greater than the recommended environmental levels, the interval of biologic monitoring shall be halved, i.e. blood analysis shall be conducted quarterly. This increased frequency shall be continued for at least 6 months after the high environmental level has been shown.

If a blood lead level of 0.060 mg Pb/100 g or greater is found, and confirmed by a second sample to be taken within two weeks, steps to reduce absorption of lead shall be taken as soon as the high levels are confirmed. Steps to be considered should include improvement of environmental controls, of personal protection or personal hygiene, and use of administrative controls. A medical examination for possible lead poisoning shall be made available to workers with unacceptable blood lead levels.

(b) Medical examination

Medical examinations should be made available prior to employee placement and annually thereafter unless a different frequency is indicated by professional medical judgment based on such factors as emergencies, variations in work periods, and prexisting health status of individual worker. These examinations should focus on the blood-forming elements, the kidney, and the nervous and reproductive systems. They should include a physical examination, complete blood counts, blood lead determinations, routine urinalysis (specific gravity, sugar and protein determinations, and microscopic examination), and should record any signs or symptoms of plumbism, if present. It should be noted that, in addition to the recommended methods for blood analysis, zinc protoporphyrin (ZPP) shows promise of being a very useful, more direct measure of lead activity. This additional blood test may be considered as an adjunct to the biologic monitoring program.

Each employee who absorbs unacceptable amounts of lead as indicated by biologic monitoring shall be examined as soon as practicable after such absorption is demonstrated and confirmed, and at least every 3 months thereafter until blood lead levels have returned to below the acceptable limit, i.e. below 0.060 mg/100 g of blood. If clinical evidence of

plumbism is developed from these medical examinations, the worker shall be kept under a physician's care until the worker has completely recovered or maximal improvement has occurred.

Medical records shall include information on all biologic determinations and on all required medical examinations. These records shall be available to the medical representatives of the employer, of the Secretary of Labor, of the Secretary of Health, Education, and Welfare, and, at the employee's request, to the employee's physician. These records shall be kept for at least 30 years after the last occupational exposure to inorganic lead.

Section 3 - Labeling (Posting)

Areas where exposure to lead at levels greater than one-half the workroom air standard is likely to occur shall be posted with a sign reading:

LEAD (Pb)

DANGER!

High concentrations of fume or dust
may be hazardous to health.
Provide adequate ventilation.

If environmental levels are at or greater than the environmental limit, or if a variance permitting use of respiratory controls has been granted, add information to the label or placard describing the location of the respirators.

Section 4 - Personal Protective Equipment and Work Clothing

The employer shall use engineering controls if needed to maintain concentrations of airborne inorganic lead at or below the limits specified in Section 1 (a) and shall provide protective work clothing as specified in subsection (b) of this Section. When the limits of exposure to inorganic lead prescribed in Section 1 (a) cannot be met by limiting the concentration of inorganic lead in the work environment, an employer must utilize, as provided in subsection (a) of this Section, a program of respiratory protection to effect the required protection of every worker exposed.

(a) Respiratory Protection

Engineering controls shall be used wherever feasible to maintain inorganic lead concentrations at or below the prescribed limits. Compliance with the prescribed limits by the use of respirators is allowed only when inorganic lead concentrations are in excess of the workplace environmental limit because required engineering controls are being installed or tested, when nonroutine maintenance or repair is being accomplished, or during emergencies. Appropriate respirators as described in Table I-1 shall only be selected and used pursuant to the following requirements:

(1) For the purpose of determining the class of respirator to be used, the employer shall measure the atmospheric concentration of inorganic lead in the workplace initially and thereafter whenever process, worksite, climate, or control changes occur which are likely to increase the inorganic lead concentration.

(2) The employer shall ensure that no employee is exposed to inorganic lead above the recommended limit because of improper respirator selection, fit, use, or maintenance.

(3) Employees experiencing breathing difficulty while using respirators shall be referred to a physician for evaluation. This evaluation should investigate if the employee has adequate ventilatory capacity, any evidence of obstructive lung disease, and the employees ability to use negative or positive pressure respirators.

(4) A respiratory protective program meeting the requirements of 29CFR 1910.134 and 30 CFR 11 which incorporate the American National Standards Institute Practices for Respiratory Protection Z88.2-1969 shall be established and enforced by the employer.

(5) The employer shall provide respirators in accordance with the Table I-1, below and shall assure that the employee uses the respirator provided at all times when the concentration of inorganic lead exceeds the permissible limit.

(6) If both fume and dust are present, the recommended usage is that for fume.

(7) The employer shall provide respirators in accordance with Table I-1 and shall ensure that the employees properly use the respirators provided when wearing respirators is required. The respiratory protective devices provided in conformance with Table I-1 shall be those approved by NIOSH and the Mining Enforcement and Safety Administration (MESA) as specified under the provision of 30 CFR 11.

(8) The employer shall ensure that employees are properly instructed in the use of respirators assigned to them and on how to test for leakage, proper fits, and proper operation.

TABLE I-1

Requirements for Respirator Usage

at Concentrations Above the Standard

Airborne Particulate Concentration of Lead	Required Respirator
Not in excess of 0.5 mg/m^3	Any dust and mist respirator, except single-use.
Not in excess of 1 mg/m^3	Any dust and mist respirator, except single-use respirator or quarter mask.
	Any fume respirator or high efficiency particulate filter respirator.
	Any supplied-air respirator.
	Any self-contained breathing apparatus.
Not in excess of 5 mg/m^3	A high efficiency particulate filter respirator with a full facepiece.
	Any supplied-air respirator with a full facepiece.
	Any self-contained breathing apparatus with a full facepiece.
Not in excess of 100 mg/m^3	A powered air-purifying respirator with a high efficiency particulate filter.

	A Type C supplied-air respirator operated in pressure-demand or other positive-pressure or continuous-flow mode.
Not in excess of 200 mg/m^3	A Type C supplied-air respirator with a full facepiece operated in pressure-demand or other positive-pressure mode or with a full facepiece, helmet or hood operated in continuous-flow mode.
Greater than 200 mg/m^3 or entry and escape from unknown concentrations	Self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive-pressure mode.
	A combination respirator which includes a Type C supplied-air respirator with a full facepiece operated in pressure-demand or other positive-pressure or continuous-flow mode and an auxiliary self-contained breathing apparatus operated in pressure-demand or other positive-pressure mode.
Fire-Fighting	Self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive-pressure mode.

(b) Work Clothing

(1) Coveralls or other full-body protective clothing shall be worn in areas where there is occupational exposure to inorganic lead. Protective clothing shall be changed at least daily at the end of the shift and more frequently if it should become grossly contaminated.

(2) The employer shall ensure that all personal protective devices are inspected regularly and maintained in clean and satisfactory working condition.

(3) Work clothing and shoes shall not be taken home by employees. The employer shall provide for maintenance and laundering of protective clothing.

(4) The employer shall ensure that precautions necessary to protect laundry personnel are taken when soiled protective clothing is laundered.

Section 5 - Appraisal of Employees of Hazards from Inorganic Lead

(a) Each employee exposed to lead shall be apprised at the beginning of his employment or assignment to a lead area of all hazards, relevant symptoms, appropriate emergency procedures, and proper conditions and precautions for safe use or exposure and shall be instructed as to availability of such information which shall be kept on file, including that prescribed in (b) below, and shall be accessible to the worker at each place of employment where lead is involved in unit processes and operations.

(b) Information as specified in Appendix III shall be recorded on U.S. Department of Labor Form OSHA-20, "Material Safety Data Sheet", (see page IX-4 and IX-5), or on a similar form approved by the Occupational Safety and Health Administration, U.S. Department of Labor.

Section 6 - Work Practices

(a) Emergency Procedures

(1) Procedures including fire fighting procedures shall be established and implemented to meet foreseeable emergency events.

(2) Respirators shall be available for wearing during evacuation procedures if long distances need to be traversed; supplied air respirators shall be available for employee use where equipment or operations cannot be abandoned.

(b) Exhaust Systems

Where a local exhaust ventilation and collection system is used, it shall be designed and maintained to prevent the accumulation of lead dust and fume.

(1) Hazardous types of exposure should not be scattered throughout a plant but, rather, concentrated in a single area where special control procedures can be utilized.

(2) Air from the exhaust ventilation systems shall not be recirculated into the workroom, and should not be discharged outside the plant so as to create an air pollution problem.

(c) General Housekeeping

(1) Vacuuming shall be used wherever practicable and no dry sweeping or blowing shall be performed.

(2) Emphasis shall be placed upon cleanup of spills, periodic repair of equipment and leaks, proper storage of materials, and collection of lead-containing dust.

Section 7 - Sanitation

(a) Food preparation, dispensing (including vending machines), and

eating shall be prohibited in lead work areas.

(b) Work and street clothing should not be stored in the same locker.

(c) Smoking or smoking materials shall not be permitted in areas where exposure to inorganic lead may occur.

Section 8 - Monitoring, Recordkeeping, and Reporting Requirements

Workroom areas where it has been determined, on the basis of an industrial hygiene survey or the judgment of a compliance officer, that environmental levels do not exceed half the environmental standard shall not be considered to have inorganic lead exposure. Records of these surveys, including the basis for concluding that air levels are below half the environmental standard, shall be kept. Surveys shall be repeated at least annually and within 30 days of any changes likely to result in increased concentrations of airborne inorganic lead.

(a) Employers shall monitor environmental levels of inorganic lead at least every 6 months, except as otherwise indicated by a professional industrial hygiene survey. If environmental levels are at or above the standard, enviromental levels shall be monitored every 3 months. This increased frequency of monitoring shall be continued at least 6 months (i.e. two more quarterly monitoring periods) after the last sampling that demonstrated levels at or above the environmental limit.

Periodic environmental sampling shall be performed to coincide with periodic biologic sampling, i.e. shall be performed within 2 weeks of biologic sampling.

Breathing zone samples shall be collected to permit construction of a time-weighted average exposure for every operation.*

(b) Records shall be maintained for all sampling schedules to include the sampling methods, analytical methods, type of respiratory protection in use (if applicable), and the concentrations of inorganic lead in each work area. Records shall be maintained so that they can be classified by employee. Each employee shall be able to obtain information on his own environmental exposure.

(c) Medical records shall include information on all biologic determinations and of all required medical examinations. These records shall be kept for at least 30 years following the last occupational exposure to inorganic lead.

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*Guidance for establishing worker exposure measurements are given in DHEW(NIOSH) Publication No 77-173, Occupational Exposure Sampling Strategy Manual, available from the Division of Technical Services, 4676 Columbia Parkway, Cincinnati, Ohio 45226.

II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon which were prepared to meet the need for preventing occupational diseases arising from exposure to inorganic lead. The criteria document fulfills the responsibility of the Secretary of Health, Education, and Welfare, under Section 20(a)(3) of the Occupational Safety and Health Act of 1970 to ". . . develop criteria dealing with toxic materials and harmful physical agents and substances which will describe . . . exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

The National Institute for Occupational Safety and Health (NIOSH), after a review of data and consultation with others, formalized a system for the development of criteria upon which standards can be established to protect the health of workers from exposure to hazardous chemical and physical agents. It should be pointed out that any recommended criteria for a standard should enable management and labor to develop better engineering controls resulting in more healthful work practices and should not be used as a final goal.

These criteria for a standard for inorganic lead are in a continuing series of criteria developed by NIOSH. The proposed standard applies only to the processing, manufacture, and use of lead products as applicable under the Occupational Safety and Health Act of 1970.

The occupational safety and health aspects of the mining and milling of lead ores are covered by provisions of the Federal Metal and Non-metallic Mine Safety Act (30 U.S.C. 725 et seq.) under which provisions the Bureau of Mines has responsibility.

These criteria were developed to assure that the standard based thereon would (1) protect against development of acute and chronic plumbism, (2) be measureable by techniques that are valid, reproducible, and available to industry and governmental agencies, and (3) be attainable with existing technology.

III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

In excess of a million tons of lead are processed yearly. The total usage of lead has remained relatively stable during recent years, but the consumption by various industries has changed. For example, there has been a decrease of lead usage in the manufacture of house paints and a simultaneous increase in the manufacture of lead storage batteries. The particular properties of lead (Table X-1[1]) have made it useful for many applications.

Scrutiny of Table X-2 (from U. S. Bureau of Mines[2]) gives an idea as to the relative proportion of lead usage for various industries. Metal products and miscellaneous categories account for the bulk of lead consumption. The refining and processing necessary to form these products include heating, grinding, and volatilization and therefore produce potentially hazardous industrial atmospheres. The impression should not be left that all workers in these industries are jeopardized, but rather that such uses of lead places them at risk of lead absorption.

Table X-3 (Gafafer[3]) lists specific occupations and trades where lead exposure occurs. The diversity of occupations displayed in these tables shows why a precise measure of the extent of lead exposure is non-existent. The National Academy of Sciences' recently published document on lead[4] agrees, stating, "A reliable definition of the extent of risk of occupational lead exposure is unavailable." Because of the changing usage of lead in industry and the widely varied trades where exposure occurs, the United States has no reporting system whereby the prevalence of occupational lead poisoning can be analyzed.

Consider Table X-4[5] which gives examples of general exposure from industrial operations utilizing lead. Simultaneous examination of these tables should give at least a general overview of the extent of occupational exposure to lead. Specific levels for operations within lead-using industries are presented in Part IV, Environmental Data.

Historical

Lead has been used for thousands of years because of its availability and desirable properties. Its low melting point (327 C), ductility, malleability, and weathering resistance enabled its use without the need for the more complex equipment that, in modern times, has enabled the use of other metals such as steel that have more desirable properties for many applications.

In the 1800's, there was an increasing recognition of hazards to health associated with lead. It was found that lead could be absorbed by inhalation and ingestion, and that lead absorption was responsible for loss of movement in printers' fingers exposed to heated lead type and for "dry grippes" in pottery and glass workers. In 1839, Tanquerel des Planches[6] published a treatise on lead diseases, to which Dana later added notes on the effects of using lead pipes. Progress in recognizing signs of lead absorption was made during the 19th Century also. Burton,[7] described in 1840 the "Burtonian Line", a blue line on the gums, as a sign of lead absorption, and chemical methods for detection of lead in blood or urine were developed.

The prevalence of lead poisoning in ancient times is speculated upon, and it has been suggested that Rome fell because of the prevalence of lead

poisoning (plumbism) in its citizens. It seems likely that, with the ignorance that existed on the hazards of lead and on methods of limiting exposure, there was a significant incidence of plumbism until its recognition in recent times generated preventive procedures.

Effects on Humans

A description of effects of lead absorption can be graphic if based on effects seen in industries earlier in this century. Thus, Mayers[8] can describe effects of lead poisoning, from studies of many years ago, such as loss of appetite, metallic taste in the mouth, constipation and obstipation, anemia, pallor, malaise, weakness, insomnia, headache, nervous irritability, muscle and joint pains, fine tremors, encephalopathy, and colic. In lead colic, there may be severe abdominal pain, such that abdominal surgery has occasionally been performed. In workers, as pointed out by Mayers,[8] who have had repeated attacks of lead colic over many years, there is a tendency towards the occurrence of weakness of extensor muscle groups. This weakness may progress to palsy, often observed as a characteristic "wrist drop" or "foot drop."

The important routes of absorption of lead by man and animals are ingestion and inhalation. Eating of lead-bearing paint by children and drinking of lead-contaminated, illicitly distilled whiskey are important sources of non-industrial poisoning. Other sources include exposure to buring battery casings, drinking of liquids from improperly fired, lead-glazed containers, and high levels of airborne lead. But man absorbs lead in small amounts not normally leading to poisoning from his food and water, and from the air. These sources lead to the "normal" body burden

of lead. Thus, the lead absorbed in the course of occupational exposure is superimposed on lead abosrbed from other means.

Descriptions of lead poisoning appear in many texts and reviews, for example Airborne Lead in Perspective, a report of the National Academy of Sciences,[4] and The Diseases of Occupations by Hunter.[9] The rest of this section pertains to the occupational aspects of lead poisoning, with a few notes on effects seen only in children.

Lead can interfere with the synthesis of heme, thereby altering the urinary or blood concentration of enzymes and intermediates in heme synthesis or their derivatives. Thus, lead poisoning can lead to accumulation of non-heme iron and protoporphyrin-9 in red blood cells, an increase in delta-aminolevulinic acid (ALA) in blood and urine, an increase in urinary coproporphyrin, uroporphyrin, and porphobilinogen, inhibition of blood ALA-dehydratase (ALA-D), and an increased proportion of immature red cells in the blood (reticulocytes and basophilic stippled cells).

Anemia from lead poisoning is associated with a reduced red cell life span and with reticulocytosis and basophilic stippled cells in peripheral blood. Symptoms of this anemia include irritability, fatigue, pallor, and sallow complexion. Bone marrow preparations show increased numbers of sideroblasts, and this is useful in differential diagnosis of lead poisoning from iron deficiency anemia.

Gastrointestinal sequelae of lead poisoning include intestinal colic, nausea often without vomiting, and constipation (or, occasionally, diarrhea). Headache usually occurs before or about the time of onset of colic.

Peripheral and central nervous system effects occur in severe poisoning. Peripheral neuropathy of lead poisoning involves considerable loss of motor function but little loss of sensory function. Extensor muscles of the hand and feet are often involved; extensor weakness normally precedes wrist drop or palsy.

Encephalopathy may be either acute or chronic. Acute encephalopathy may follow ingestion or inhalation of large amounts of lead, and may develop quickly to seizures, coma, and death from cardiorespiratory arrest. Chronic encephalopathy usually occurs in children after excessive ingestion of lead, and leads to loss of motor skills and of speech, and to development of behavioral disorders. Lead encephalopathy, often involving psychosis, also occurs from absorption of alkyl lead compounds.

Nephropathy is another effect of lead poisoning. There may be a progressive and irreversible loss of kidney function, with progressive azotemia, and occasionally hyperuricemia with or without gout. Children have developed renal dwarfism, hypertension, marked retention of urea, and low urinary concentration; some children with acute encephalopathy have developed a form of Fanconi syndrome, a kidney disease indicative of severe injury of the promixal renal tubules. Nephritis in adults is not common, but ischemic nephritis may occur after prolonged absorption of lead.

Epidemiologic Studies

Lane[10] examined the causes of death of storage battery workers, including retired workers, and compared data from this group with data from all English and Welsh males of similar ages during the same period of time. Among the retirees who had been exposed to lead, there were found to be greater numbers of deaths than would have been expected, for their ages, from data on the population as a whole. Most of this excess in expected mortality was accounted for by vascular lesions in the central nervous system. Lead workers who died during employment also showed an excess of deaths from this cause.

Another study of electric storage battery workers was conducted by the Public Health Service over 30 years ago.[11] In this study, the incidence of various disease states was studied in relation to lead exposure of 766 workers, most of whom (75%) had worked in storage battery plants for more than five years and some of whom (12%) had worked there for twenty years or more. The incidence of disease (other than plumbism) in men exposed at levels of 0.15 mg/m^3 and higher (high exposure group) was compared to the incidence in men exposed below 0.15 mg/m^3 (low exposure group). Special attention was given to cardiovascular disease because of the common belief that chronic plumbism results in arteriosclerosis; however, the data developed by the PHS team did not show that more severe exposure to lead is associated with a significantly higher incidence of vascular disease. The incidence of arteriosclerotic-hypertensive disease was not significantly different in the high and low exposure groups. The responses to a standard

exercise, in terms of return to pre-exercise pulse rates and to systolic and diastolic blood pressure, were also compared, and again the two groups were found not to be significantly different from each other. These lead workers were also found not to be significantly different from other, non-lead, workers in terms of blood pressure. From this, it was concluded that exposure to lead in the storage battery industry does not cause cardiovascular effects.

A contrary conclusion was reached by Dingwall-Fordyce and Lane[12] in a study of British battery workers. A significant excess of deaths from cerebrovascular accidents was found in pensioners who had had exposure to lead of sufficient degree to have caused mean urinary lead levels of 0.25 mg/liter during many years of lead work. They compared three groups of workers--those with no occupational lead exposure, those with negligible exposure, and those occupationally exposed to lead*--with the general population of English and Welsh males of similar ages. They found a significant excess of death, over that predictable from the population at large, among retirees in the highest exposure group, and this was largely attributable to cerebrovascular accidents. They also examined records of deaths due to cancer in lead workers, both employed and retired, and concluded that there was no association between malignant disease and lead absorption. While they found an excess of deaths from cancer in the negligible exposure group (in the last decade of the 35-year figures only), there was

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*Urinary lead levels in this group averaged between 0.10 and 0.25 mg/liter for a 20-year period.

a slight decrease in deaths, from that expected from statistics on the whole population, among workers absorbing more than negligible amounts of lead, hence their conclusion that malignant disease is not related to lead absorption. As improved working conditions decreased lead exposure, the excess of cerebrovascular deaths diminished.

Malcolm[13] recently conducted similar investigations of past and present employees exposed to lead. Since 1927, airborne lead to which these men had been exposed had been limited to 0.15 mg/m^3, according to Malcolm. He divided the workers into three groups: (A) no exposure, (B) mild exposure, and (C) severe exposure. Average blood lead* in group (C) workers, since 1961, has been 0.065 mg/100 g, from which it may be inferred that the 0.15 mg/m^3 air concentration was sometimes exceeded. Urinary leads in subgroups averaged 0.09 to 0.180 mg/liter, and averaged 0.119 mg/liter for the entire group of workers.

Based on comparison of blood pressures of the two exposed groups (B and C) with the control group (A), it was concluded that there was no occupationally induced hypertension (although there might have been lead-induced hypertension before improved hygienic measures were instituted). There was a non-significant increase in chest disease among older retired workers, attributed to other causes, since most of these pensioners lived in an urban area with a higher rate of death from chest disease than that in the country as a whole.

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*Concentrations of lead in blood are expressed as weight units (such as mg) per 100 ml or 100 g of whole blood. European workers more commonly express blood lead as weight units per 100 ml of blood, while American workers more commonly express blood lead as weight units per 100 g of blood. This document will follow the American custom except in referring to studies reporting blood lead in weight units per 100 ml. The difference between the two expressions is small, about 5% or less. Thus, a blood lead concentration of 0.080 mg/100 g would be equivalent to about 0.084 mg/100 ml.

Unlike the findings of earlier investigators (Dingwall-Fordyce and Lane,[12] and Lane[10]) Malcolm found no evidence of increased frequency of cerebrovascular death in his study, which included deaths occurring between 1963 and 1967, while data from the two earlier reports included deaths from 1926 to 1960. Thus, if all three reports are correct in their conclusions, it would seem that improving hygiene has diminished lead-induced cerebrovascular disease.

For years, chronic nephritis was thought to be a consequence of plumbism, and an analysis of death rates in the U.K. in 1921[10] and in 1931[13] shows a considerable excess in plumbers and painters due to nephritis and to cerebrovascular disease. The question of nephropathy from lead has also been raised by Henderson and Inglis,[14] who showed a relationship between chronic nephritis and excessive lead absorption as indicated by elevated lead levels in bone.

Lane[15] described 9 deaths from renal failure in lead workers, men who had been exposed for long periods at lead concentrations around 0.5 mg/m^3. Terminally, they all had evidence of chronic azotemic nephritis. These men, all of whom worked in storage battery industries for over 20 years, died between the ages of 42 and 52 (average age at death was 48.4). Other than two episodes of colic, there had been no previous history of lead intoxication.

In the United States, there have been few reports of renal disease in lead workers,[13] though the PHS survey of storage battery workers discovered an increased incidence of albuminuria in affected workers.

Animal Toxicity

Unlike toxicologic studies of many industrial substances, experimental animal studies of either inorganic or organic lead have contributed far less to an understanding of the toxicology of lead and its compounds than studies on man, and hence have directly contributed very little to the criteria for the standard for lead. The reason is that until recently, much of the investigative effort was directed to the effects of lead on the red blood cell, its urinary intermediates and lead content of blood and urine, all readily investigated in man. Moreover, many of the studies in man or animals relate to detecting changes in biologic constituents of the blood and urine, and hence are relevant more to criteria for biologic standards than to air standards. Thus, the experimental studies discussed herein will be confined to those that confirm or extend the findings in man in these areas and which are related, even if only indirectly, to the criteria for the air standard.

In recent years, research investigations have broadened to include biologic systems other than the erythropoietic, and in this way may ultimately provide new criteria for standards. Lead intoxication has been studied for its effects on the rat thyroid, comparative changes in kidneys of rat and man, and the effect of certain trace metal deficiencies on the toxicity of lead. But only a beginning has been made in our understanding of the action of lead on the nervous system; behavioral effects have been studied in rats following exposure to tetraethyl lead after the finding of marked metabolic changes in the brain from its administration.

a. Experimental Animal Toxicology. The USPHS-sponsored conference on environmental lead[16] in 1965, although oriented towards the community

environment, marked a turning point in experimental animal investigations on lead. Up to this time, animal studies relating to standards criteria used hematologic disturbances for the most part as a focal point of investigations because of their practical usefulness as criteria for judging harmful exposures to lead.

b. Biosynthesis of Heme. Following the first evidence by Rimington[17,18] that lead interfered with the incorporation of iron into the protoporphyrin molecule, and the subsequent demonstration by Eriksen[19] and others that lead also interfered with an early step in heme synthesis catalyzed by delta-amino-levulinic acid dehydratase (ALA-D), Kreimer-Birnbaum and Grinstein[20] confirmed in rabbits poisoned by lead the earlier findings of Eriksen and others. As determination of ALA-D in the red blood cell became recognized as the most sensitive criterion of response to lead exposure yet discovered, it was applied to the control of lead exposures among industrial workers. It was soon suspected, however, when red cell ALA-D was markedly inhibited in the absence of subjective symptoms of lead poisoning and at blood levels within currently accepted normal limits[21-23] that, as a criterion for overexposure of lead workers, ALA-D was of less value than had been anticipated. Studies in dogs[23] confirmed this suspicion; dogs that had been given lead acetate for a period (46 weeks) until their red cell ALA-D was nearly or completely inhibited and were bled to a reduction of from 30 to 40% in hemoglobin, red cell count and hematocrit ratio, recovered to normal hematologic values as well as did controls not treated with lead. Thus, animal studies resolved the important issue of the relative usefulness of the measure, reduction in red cell ALA-D, as an indicator of response to lead exposure, and hence as a criterion for a lead standard, albeit a criterion only indirectly related to an air standard; measurement of changes in ALA-D is too sensitive

to be usefully applied to workers exposed to lead at this stage of knowledge.*

c. Other Animal Studies on Hematologic Effects of Lead. In addition to the inhibitory effects of lead on the biosynthesis of heme, animal studies have included 1) the stimulation of erythropoietic activity[24]; 2) increased rate of basophilic stippling[15]; 3) reticulocytosis[25]; 4) concentration of coproporphyrins in urine and certain tissues[26]; and 5) the effect of lead on iron metabolism in hemoglobin formation.[27]

d. Serum Protein Changes. Changes in the patterns of the proteins in human blood serum, consisting of a decrease in albumin-globulin ratio with marked increases in the alpha- and beta-globulins, have been confirmed in animals.[28]

Similar confirmation has been made in animals of the findings in man of reduced quantities of mucoid and sialic acid, prosthetic groups of conjugated proteins,[29] reductions of which were used as a warning of impending lead poisoning in industry. Unfortunately, other common conditions such as inflammation also cause changes in the amounts of these blood constituents.

A distinct relationship has been found between lead poisoning and the metabolism of nicotinic acid[30]; animals poisoned by lead showed a marked decrease in the nicotinic acid content of blood (and urine), indicating an increased utilization of this constituent by lead, and suggesting that lead exerts serious effects on the pyridine nucleotides, either by blocking

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*This is not to detract from the major recommendation of the PHS conference on lead[16] to search for ever-more sensitive indicators of response, because much of value on the mechanism of lead in the biosynthesis of heme has resulted, but it does clearly point out 1) that ultra-sensitive methods may not always have practical utility in estimating and controlling workers exposure, and 2) that, inasmuch as highly sensitive methods are used as the criteria for many, if not most, of the air standards in the U.S.S.R., these standards must be carefully reexamined in the light of their appropriateness and suitability.

their synthesis or by accelerating the degradation of nicotinic acid. These changes have been suggested as a means of assessing the severity of lead poisoning.

In line with the general opinion that toxic substances adversely affect the body's resistance to disease by interfering with natural immunologic processes, Fonzi et al.[31] showed that lead-treated and actively immunized animals developed lesser amounts of gamma globulin than did immunized controls. Similarly, lysozyme, another part of the defense mechanisms of the body, was progressively reduced in the blood serum of dogs administered lead salts for a prolonged period.[32]

Although shifts in the body's inorganic elements (copper, calcium phosphorus, sodium and potassium[33]) from lead poisoning have been reported,[34] their significance in over-all body metabolism is yet to be clearly demonstrated.

e. Endocrine Changes. The effects of lead exposure on some aspects of endocrine function have been studied in animals, as well as in man. The excretion of steroids was studied in the urine under different conditions of lead exposure in the hope of finding some evidence of their relation to lead absorption. Adrenal steroids were reported at first to decrease, then to increase considerably during advanced stages of lead intoxication.[35] Vitamin C content of the adrenal gland was decreased in the guinea pig following exposure to lead.[36]

Relatively little use has been made of animals in the study of other endocrine functions, these functions being readily studied in man. Sandstead[37] has, however, reported that lead, like other heavy metals, impairs the uptake of iodine by the thyroid, and that the conversion of iodine to protein-bound iodine is retarded; females were more affected than males.

f. Renal Changes. Goyer[38] has recently reviewed the current state of knowledge of the effects of lead on the kidney; his review is based in large part on his investigations and those of his associates. Prominent among their findings of acute lead poisoning in animals were 1) formation of intranuclear inclusion bodies, 2) mitochondrial swelling with impairment of oxidative and phosphorylative processes, and 3) aminoaciduria (apart from the long-recognized delta-aminolevulinic aciduria); the intranuclear inclusion bodies were a lead-protein complex that may have adaptive function in excessive lead exposure. The acute renal changes progress to a diffuse nephropathy with tubular atrophy and dilation. Rats developed hyperuricemia and in chronic lead poisoning, renal adenocarcinoma. In all but the last, the findings made in rats paralleled those seen in man.

g. Trace Metal Interactions. In recognition that lead poisoning is often associated with an iron-deficiency anemia, the interaction of lead on iron deficiency was studied in the rat.[39] An enhancement of lead retention and toxicity was found in the iron-deficient animals as measured by elevated ALA excretion.

h. Effects on the Nervous System. Despite the fact that the nervous system can be affected by lead, comparatively little experimental attention has been directed to gaining an understanding of the manner in which lead acts on this system. Behavioral response studies in animals, predominantly by Soviet scientists, comprise most of the research effort, although of late, Xintaras and associates have initiated investigations in behavioral toxicology.

Using a range of atmospheric concentrations of lead oxide dust, Gusev[40] found that at a level of 11 $\mu g/m^3$ disturbed reflexes began to occur at 1.5

to 2 months of exposure, whereas no impairment of reflexes was seen at levels averaging about 1 $\mu g/m^3$; base-line conditioned reflex activity returned 10 to 23 days after cessation of exposure. Although no changes in the formed elements of the blood were seen, despite a lead content in rat bone of 10-fold higher than that of animals on the lower dose, histopathologic changes in the central nervous system were seen in both rats and rabbits at the 11 $\mu g/m^3$ level.

Shalamberidze[41] reported disturbed conditioned reflexes in rats exposed to lead sulfide ore dust at a level averaging 48 μg Pb/m^3, 6 hours daily for 6 months. However, because of the insolubility of the sulfide supported by health experience with lead sulfide, responses to lead sulfide at that level are unlikely.

Xintaras studied the applicability of evoked response in the rat's cortex in air pollution toxicology[42,43]; in rats intoxicated with lead acetate he found electroencephalographic changes similar to changes in man.[43] From studies of alterations in rapid eye movements during sleep, he concluded that lead may cause impaired neural control in rats.[43]

i. Developmental Effects. Although mice nursing on dams fed diets containing high levels (1% or 4%) of lead carbonate showed evidence of faulty growth and various neurologic changes,[44] recent evidence reveals a low degree of teratogenic effects in rats and mice.[45]

Correlation of Exposure and Effect

Tsuchiya and Harashima[46] studied storage battery workers and compared airborne lead with urinary lead, urinary coproporphyrin, basophilic stippling of erythrocytes, and specific gravity of blood as indications of anemia.

To control urinary coproporphyrin to normal levels (below 50 μg/liter), they recommended a TLV of about 0.12 mg/m^3 for daily 8- to 10-hour exposures. However, the workers studied by these investigators worked 48 to 60 hours a week. With the increased lead absorption from these working hours, a lower standard than that suitable for a 40-hour week would be indicated. If other criteria were chosen on which to base an air limit, other limits would have been selected; 0.10 mg/m^3 would have been recommended to keep urinary lead levels below 0.15 mg/liter, 0.14 mg/m^3 to keep basophilic stippling at 0.3 per thousand, and 0.14 to 0.15 mg/m^3 to prevent anemia. They did not use blood lead as a criterion of effect.

The study of Williams, King, and Walford[47] was based on observations of storage battery workers who worked a 40-hour week, and were stable in their exposure. They had worked without job change for a year, there was no recent absence for sickness or vacation, and no change in overtime or productivity for 6 months.

Workers in the plastics department were exposed to airborne lead levels of about 0.01 mg/m^3, while workers in lead handling departments were exposed to higher levels, up to about 0.3 mg/m^3. Specific gravities of urine samples averaged 1.020 in the morning and 1.022 at lunch time. They concluded that air levels of 0.20 or 0.15 would result in the blood and urinary lead levels given in Table X-5 (urinary lead levels were corrected for a specific gravity of 1.024; it should be noted that a urinary level of 0.20 mg/liter corrected to a specific gravity of 1.024 would be 0.133 mg/liter corrected to 1.016).

These investigators also showed a very low correlation ($r = 0.09$) between airborne lead and blood hemoglobin levels.

Selander and Cramer[48] compared blood lead, urinary lead, and urinary ALA in lead workers. They found several workers with high urinary lead and ALA values in relation to blood lead and attributed this to a metabolic influence of lead; ALA excretion in these workers had seldom fallen to normal values. They recommended that workers removed from lead overexposure not be allowed to return until ALA excretion was normal.

A statement by a group of experts (R.E. Lane, D. Hunter, D. Malcolm, M.K. Williams, T.G.F. Hudson, R.C. Browne, R.I. McCallum, A.R. Thompson, A.J. deKretser, R.L. Zielhuis, K. Cramer, P.S.I. Barry, A. Goldberg, T. Beritic, E.C. Vigliani, R. Truhaut, R.A. Kehoe, and E. King)[49] on diagnosis of inorganic lead poisoning suggests ranges of indices of lead absorption for occupationally acceptable exposures with the following upper limits:

Blood lead: 0.08 mg/100 ml
Urinary lead: 0.15 mg/liter
Urinary coproporphyrin: 0.50 mg/liter
Urinary ALA: 20 mg/liter

They point out that these values may not be applicable when there are low hemoglobin levels or where chelating agents have been used.

Stankovic[50] reported on blood and urine lead concentrations, urinary coproporphyrin, and urinary ALA in workmen exposed to lead at various concentrations of lead in air. In workmen exposed to 0.15 mg/m^3 and below, the highest individual blood lead found was 0.06 mg/100 g, the highest urine lead 0.12 mg/liter, the highest urinary coproporphyrin 0.186 mg/liter, and the highest urinary ALA 11.85 mg/liter. There were 48 workers exposed to air lead levels of 0.025 to 0.15 mg/m^3, whose mean blood lead level was 0.05 mg/100 g (range of 0.03 to 0.06). However, the number of workers exposed to or near 0.15 mg/m was not stated.

Zielhuis[51] has reviewed and analyzed the data of several other investigators of human absorption of lead, in terms of the relationships between blood lead, ALA, and coproporphyrin. He concluded from analysis of these data that a combination of blood lead greater than 0.08 mg/100 g with values of urinary lead greater than 0.15 mg/liter or urinary ALA greater than 20 mg/liter or urinary coproporphyrin greater than 0.80 mg/liter is evidence of an unacceptable degree of occupational exposure to lead. He did not review the relationships between airborne lead and the several indices of biological effect of absorbed lead.

The selection of 0.08 mg Pb/100 g of whole blood has been described by Kehoe[52] as the critical concentration of lead in blood below which no case of even mild poisoning has been induced by lead. The higher the concentration of blood lead above 0.08, the greater the likelihood of lead poisoning, though higher concentrations did not mean lead poisoning in all individuals. The scientific consensus supports the view of Kehoe as it applies to adults.

However, even in the hands of the best analyst, there may be a 10% error in a specific lead determination. Thus, an analysis showing a blood level of 0.08 mg/100 g may have a true value of almost 0.09. This may account for the recommendation of some authorities[48] that blood lead levels be kept below 0.07 mg/100 g.

IV. ENVIRONMENTAL DATA

Information presented in this section was selected to satisfy two purposes: (1) link measured environmental and biological levels to specific lead using industries, and (2) to link exposure levels to clinical lead intoxication. Table X-4 (from Elkins[5]) gives an overview of in-plant lead levels from various industries. Specific data for industries and a discussion of the exposures therein follow. The principal plant types covered are printing, storage battery manufacturing, and welding operations. Note that the general concentrations of lead in in-plant air range from negligible to those indicative of imminent danger. Scrutiny of specific plant operations is necessary to determine where the hazards exist and how priorities for control should be developed.

(a) Printing

The necessary characteristics of type metal prescribe the use of lead alloys. Examinations of Table X-6 (from Brandt[53]) shows that many areas could presently comply with a 0.15 mg/m^3 standard. Others such as the remelt room and stereotype room will require additional control measures.

Table X-7 (from Ruf[54]) associates exposure levels to significant functions performed by workers in the printing industry. They are obviously not 8-hour TWA levels but are nevertheless indicative of conditions. Most of the higher exposures occur while either some mechanical action is applied either to the metal (such as drossing and filing) or near the melting pots. In the former, large amounts of dust are generated, and in the latter the lead fumes present the problem.

Table X-8 shows data of Belknap [55] on calculated exposures in printing industries. The calculations were based on time spent by printers at various tasks and used data of Ruf [54] summarized in Table X-7. Calculated air exposures and urinary lead levels are shown for various operations. These air concentrations (or urinary levels) may be erroneous, because much less urinary lead would be expected at the listed air concentrations.

(b) Storage Battery Manufacture

Tables X-9 and X-10 furnish data on levels found in plants where storage batteries are produced. The percentages of workers exposed to air-lead levels greater than 0.15 mg/m^3 is important. Table X-9 directs attention to the operations where the serious hazards occur. The levels shown are serious in that they are above the recommended concentration, but also appear to be in a range that are responsive to conventional industrial hygiene control techniques.

(c) Welding and Cutting of Steel

Welding or cutting of lead bearing steels results in the generation of lead fume in significant concentrations. This is also the case when these operations are performed on steels which are either galvanized, zinc-silicate coated, or painted with lead pigmented paints. Elkins [5] observed that at 507 C the vapor pressure of lead (VP = 0.000016 mm Hg) is high enough to produce a concentration after oxidation of 0.18 mg/m^3 of lead fume. During welding or cutting temperatures may reach 1000 to 3000 C.

Table X-11 contrasts lead fume exposures when welding galvanized steel and zinc-silicate coated steel. The worst exposures occurred when welding the zinc-silicate coated steel. Electric arc welding produced an average concentration of 5.63 mg/m^3 and oxy-acetylene produced 1.96 mg/m^3 of lead. The information presented in Table X-11 developed by Pegues.[56] Samples are well identified, providing a clear picture of lead exposure in these welding operations. Note that with good ventilation breathing zone samples can be controlled to within the recommended standard. Note also that room air samples downwind from the welder can rise to levels which jeopardize the health of other workers. In Table X-12 (from Tabershaw[57]), limited data are presented to illustrate the exposures of those workers who perform cutting operations on painted structural steels. The urinary lead data indicate that sufficient protection from lead fume is not given through the use of the indicated respirators, and further controls are needed.

(d) Workers Whose Occupational Exposure is Out-of-Doors

Policemen, firemen, taxi drivers, vehicle tunnel attendants, garage mechanics, and service station attendants are examples of occupational groups who work out-of-doors, but are nonetheless exposed to lead. The primary source of this exposure is the lead salts emitted from internal combustion engines which burn leaded gasoline. Tables X-13 and X-14 were taken from a U.S. Public Health Service survey[58] of lead in the atmosphere and describe lead levels in blood and urine. This same survey shows that these workers are placed in atmospheres containing various amounts of lead for their 8-hour workday. Few of the samples indicate levels which even approach the biologic standard; however, the distribution of the samples does demonstrate the need for monitoring these individuals for lead exposure. There are many levels shown in these tables which are in excess

of normal (not occupationally exposed) levels, and this fact shows that there is absorption of lead on the job.

(e) Miscellaneous

Limited data for lead exposures in many other industries prevent a detailed analysis here. Nonferrous foundries often utilize lead alloys. Berg and Zenz[59] reported on one such foundry and stated that atmospheric lead concentrations have risen in the past twenty years. They stated that from 108 samples collected between 1943 and 1947, there were average concentrations as follows: 0.14 mg/m^3 in the melting room and 0.18 mg/m^3 in the pouring floor area. The results from 40 samples of 1953-1954 produced the following increases: 0.28 mg/m^3 in the melting room and 0.29 mg/m^3 in the pouring floor area. Extensive modification and increased ventilation reduced the concentration from 0.28 mg/m^3 to 0.03 mg/m^3. Attention to the processes and analysis of what operations produced the high concentrations facilitated the control of the lead hazard.

Leaded steel production sometimes generates hazardous occupational exposures to lead. Ruhf[60] reported that the highest atmospheric lead concentrations prevailed during the steel pouring operation in which the lead is added. Other elevated exposures were measured in processes such as the rolling mills. However, because of the intermittent nature of the operations the time weighted average exposure was below the <u>then</u> current limit of 0.20 mg/m^3. Ruhf further described control measures and manufacturing techniques whereby lead exposure can be minimized.

V. DEVELOPMENT OF STANDARD

Basis for Previous Standards

The American Conference of Governmental Industrial Hygienists (ACGIH)[61] has reviewed previous standards for lead in the work environment, and has commented that there are few meaningful data relating to the threshold limit value, probably because most authorities rely primarily on other tests for estimating lead hazards, such as urinary and blood leads, urinary coproporphyrin and ALA, as well as examination of the blood for stippled cells.

Nevertheless, attempts were made to control occupational lead poisoning by establishing acceptable air levels to guide engineering control measures. Although the point is not documented, it seems that at one time an air limit value of 0.5 mg/m^3 was used. In the 30's and 40's, a value of 0.15 mg/m^3 was a common, but often unachieved, goal based on a recommendation of a 1928 PHS survey of storage battery workers published in 1933.[62]

This value continued to be the one most often accepted until 1957, when the ACGIH increased the TLV to 0.20 mg/m^3, based in part on data of Elkins[5] showing that exposure at 0.20 mg/m^3 would result in urinary excretion at 0.20 mg/liter.

In 1971, the Conference recommended lowering of this value back to 0.15 mg/m^3. This appears to have been based in part on the recommendations of the International Subcommittee for Occupational Health, Permanent Commission and International Association of Occupational Health[63] at a 1968 meeting in Amsterdam, and on the results of the study by Williams, King, and Walford.[47]

The International Subcommittee recommended a time-weighted average concentration for a 40-hour week of 0.15 mg/m^3, on the basis that it corresponded to an acceptable blood concentration of 0.07 mg/100 ml.

The current workroom air standard established under the Occupational Safety and Health Act of 1970 (published in Part 1910.93 of the Federal Register, Volume 36, Number 157, pages 15101-15107, dated August 13, 1971) is 0.2 mg/m^3; this is a time weighted average, and is based on American National Standards Institute Z37.11-1969.[64] This ANSI standard provided no basis for its recommendation.

Basis for Recommended Environmental Standard and Biologic Monitoring

(See Appendix V - NIOSH Testimony Presented at DOL Hearing on a Lead Standard.)

Earlier in this century, efforts to reduce occupational lead poisoning were based on adherence to hygienic workroom air guides. As more knowledge developed, increasing attention was given to blood and urinary lead levels as guides to reduction of occupational poisoning. Concomitantly, there was increasing attention to better lead analyses. There was also an increasing knowledge of the relationship between levels and rates of absorption and excretion, blood lead levels, and health status.

The PHS study by Dreessen et al.[11] was undertaken during the period that the workroom air guide of 0.15 mg/m^3 was accepted,, but failure to achieve control of airborne lead to this level was common, so findings of slight effects among workers in lead-using industries by Dreessen and co-workers did not invalidate the guide. Though not documented, it appears that many industries have rotated their workers to various jobs to keep blood lead levels below 0.08 mg/100 g; thus, exposure to unsafe workplace air levels did not result in adverse effects on health.

Consequently, there is a little definitive information from experience in the United States and other countries on the suitability of 0.15 or 0.20 mg/m^3 as an air-lead level to which workers can be safely exposed over a working lifetime.

However, much experience has accrued to show that absorption of lead in amounts resulting in blood lead concentrations of 0.08 mg/100 g or less will not lead to adverse effects on health, and there is information from studies in other countries relating airborne lead levels to blood lead.

It was previously concluded (III. Biologic Effects of Exposure; Correlation of Exposure and Effect) that a blood lead level of 0.08 mg/100 g is useful for delineating acceptable from nonacceptable lead absorption. While levels below 0.08 mg/100 g are indicative of acceptable occupational lead absorption and, if also representative of past absorption of lead by an individual person, also indicative of insignificant risk of lead poisoning, it should not be concluded that lead poisoning will occur if blood lead levels exceed 0.08 mg/100 g. However, there is an increasing risk of poisoning as levels increase above 0.08 mg/100 g, so absorption of lead should be held to amounts that will result in blood lead levels less than 0.08 mg/100 g. As Kehoe[65] has stated, "...lead poisoning occurs in man only when certain well-defined conditions have been fulfilled" and that this is quantitatively applied by "...the relationship between the current rate and the extent of the absorption of the inorganic compounds of lead, and the concentration of lead in an accessible tissue of the living body, namely, the blood." Thus, a biologic standard of 0.08 mg of lead per 100 g of whole blood is recommended; it provides a margin of safety in adults,

but probably not in children. The extent of this margin of safety is not known, but it seems likely that there will be few, if any, cases of lead poisoning below 0.09 mg/100 g.

Kehoe[65] also pointed out the usefulness of urinary lead as an index of current absorption of lead, but added that it was a quantitatively less certain index than blood lead. It may be consistent with this view that Williams, King, and Walford[47] found that the best correlation between airborne lead and biochemical index of effect was with blood lead ($r = 0.90$) and less correlation with urinary lead ($r = 0.82$). The study of Williams and co-workers[47] indicates that blood levels of 0.08 mg/100 ml is associated with a urinary lead level of 0.20 mg/liter. It has been commonly accepted that 0.20 mg/liter is a safe level in urine, based in part on the findings of Elkins.[5] However, it is important to note that Elkins' studies involved calculation of specific gravity of urine to a value of 1.024. The studies of Williams et al.[47] also calculated urinary specific gravity to 1.024. (Urinary lead levels of 0.20 mg/liter, adjusted to a specific gravity of 1.024, would be 0.133 mg/liter if the specific gravity were calculated to 1.016.) Thus, the conclusion of Zielhuis[51] that urinary lead greater than 0.15 mg/liter, uncorrected for specific gravity, represents unacceptable absorption of lead is consistent with the selection of a biologic standard for urinary lead of 0.20 mg/liter, so long as the specific gravity correction is used.

ALA and coproporphyrin assays, and blood examinations for hemoglobin, reticulocytes, and stippled cells are useful in the assessment of worker health, but are less useful than blood lead as a single criterion for

interpreting the acceptability of lead absorption, since no one of these measurements is a specific index of lead absorption, as is urinary or blood lead.

It should be emphasized that blood lead and urinary lead are good indices of current absorption of lead (in the absence of anemia or absorption of chelating agents), but are not necessarily indications of body burden of lead or of the state of health of the individual. Bone lead is probably more indicative of total body burden than is blood lead, but it is not feasible to sample bone for routine lead assay. As to state of health, overabsorption of lead by an individual in the past may have led to a high body burden of lead and may also have contributed to a state of current ill-health in the individual, all without causing currently high blood or urinary levels of lead.

Since the studies of relationship between health and airborne lead levels are inadequate, it is concluded that an air standard should be recommended from data on the relationship between airborne lead and biochemical indices of effect, most importantly, blood lead. There are several studies that point to $\sim$0.15 mg/m^3 as the level of airborne lead that will result in biochemical indices showing acceptable absorption of lead, in other words, showing that occupational exposure at 0.15* mg/m^3 will not result in adverse effects on the health of workers.

Tsuchiya and Harashima[46] studied storage battery workers in Japan and compared airborne lead with urinary lead, urinary coproporphyrin, basophilic stippling of erythrocytes, and, as an index of anemia, specific gravity of blood. They recommended airborne lead levels on the basis of acceptable

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*See appendix V for basis for revised recommendation for an occupational exposure to inorganic lead.

levels of these biochemical indices. On the basis of acceptable urinary lead levels of 0.15 mg/liter, corrected to a specific gravity of 1.024, they recommended a threshold limit value of 0.10 mg/m^3. If a higher urinary lead level is accepted, as recommended in the preceding discussion of the relationship between acceptable lead absorption and urinary lead excretion, a higher air standard would result. It should be noted that the workers studied by Tsuchiya and Harashima worked 8 to 10 hours, 6 days a week, and they observed that a higher air level would have been recommended for a 40-hour week.

The study most directly relevant to the development of a recommended workplace air standard is the study of Williams, King, and Walford.[47] Their data (Table X-5), from studies of storage battery workers stable in their employment (40-hour work week, no job change in the past year, no recent absence or sickness, no change in overtime or productivity), showed that exposure at 0.15 mg/m^3 resulted in a mean blood lead of 0.060 mg/100 ml. Were mean blood lead the criterion of effect, an air standard much higher than 0.15 mg/m^3 could be recommended, but in order to keep most or all workers' blood lead below 0.084 mg/100 ml (0.080 mg/100 g), it is believed that a mean of about 0.060 mg/100 ml should be achieved. The data of Williams and associates[47] does not provide a basis for interpreting the percentage of workers exposed at 0.15 mg/m^3 that will have blood levels above 0.084 mg/100 ml. However, it is believed that a small percentage will have blood lead levels at or above 0.084 mg/100 ml or 0.080 mg/100 g, so it is recommended that workers be monitored biologically, by periodic assays of blood lead, or of blood and urinary lead.

Stankovic[50] also compared airborne lead with blood and urinary lead, and in workmen exposed to lead at 0.15 mg/m^3 and below, the highest individual blood lead found was 0.06 mg/100 g, and the highest urinary lead 0.12 mg/liter. However, the number of workers exposed at or near 0.15 mg/m^3 was not stated, so his finding of 0.06 mg/100 g as the highest individual blood lead is not believed to contradict the previously stated inference that some workers exposed at 0.15 mg/m^3 will have blood lead levels at or above 0.08 mg/100 g (especially those workers absorbing abnormal amounts of lead from nonoccupational sources).

It is of interest that conclusions of experts[63] support the recommended standard, but since data and arguments supporting their conclusions were not presented, their recommendations have not been given weight in deriving the recommended occupational air standard.

The rationale for the recommended work practices and sanitation practices was principally derived from Kehoe.[66] They are normal industrial hygiene procedures used to control occupational exposures to various dusts and fumes.

If worker exposures exceed 40 hours a week, the same TWA of 0.15 mg/m^3 should be used unless exposures so greatly exceed 40 hours a week that nonworking (excretion) time is significantly reduced; exposures up to 50 hours a week should not significantly affect the time for excretion of absorbed lead. However, maintenance of the same TWA means a proportionate reduction in average concentration as exposures exceed 40 hours a week. To achieve a TWA of 0.15 mg/m^3, the average concentration should be 0.15 mg/m^3 for a 40-hour week and 0.12 mg/m^3 for a 50-hour week.

Basis for Environmental Sampling and Analytical Method

Various methods of sampling air and of analysis of these samples have been considered, and recommended methods are presented in Appendixes I and II.

The recommended method of sampling air involves collection of 100 liters of air or more, use of breathing zone samplers with sampling at a rate of 2 liters/min., and collection on 0.45μ cellulose membrane filters. Other sampling rates and other collection media (filter paper, nitric acid impinger, electrostatic precipitation) are capable of giving equivalent results. The recommended procedure is described in Appendix I.

For analysis of lead in blood, atomic absorption spectrophotometry[67-71] and dithizone colorimetry[72,73] were considered. Appreciable consonance can be demonstrated between results obtained with atomic absorption and dithizone methods. Both methods have been used for analysis of air samples, and both are concluded to be capable of giving accurate results. After a review of the several procedures involving atomic absorption spectrophotometry, it was concluded that no one of these procedures has been sufficiently standardized. Individual laboratories get excellent results with a specific procedure, but these procedures have not been compared in a number of laboratories. Dithizone colorimetry, on the other hand, has been used for a long time and has been thoroughly studied. The procedures, interferences, sensitivity, and replicability have been studied and are described by Keenan, Byers, Saltzman, and Hyslop.[72] The recommended procedure is described in Appendix II.

Dithizone colorimetry is a wet chemical method requiring equipment found in most chemical laboratories, but requires meticulous attention to detail and to the prevention of loss and the exclusion of contamination.

Results of lead analysis by this method obtained by well trained technicians are often superior to results obtained by other methods of analysis.

Basis for Biologic Analytical Method

Blood lead was selected as the best method, and urinary lead as an acceptable method, for judging lead absorption, for reasons discussed in earlier sections (see "Basis for Recommended Environmental Standard and Biologic Monitoring").

Specific details for collection of biologic specimens for lead analysis have been described in a booklet Methods for determining lead in air and in biological materials, published by the American Public Health Association. Keppler et al.[75] described the initiation of interlaboratory evaluations of lead in an attempt to improve accuracy and reproducibility of laboratory analyses through a system of accreditation. Subsequent reports[76,77] have described some of the results, from which it is apparent that lead analysis is subject to significant error unless a very high degree of care is used.

Methods for the collection of blood and urine are described by Keenan et al.[72] (Appendix II). While lead-free Vacutainers are convenient, any lead-free tube can be used for collection and shipment or storage of blood prior to analysis. No aliquots can be taken unless blood-clotting has been prevented, either by taking aliquots before clotting or by prevention of clotting, e.g., by heparinization. Single use needles ("throw-aways") are acceptable, but must be lead-free, thus must not be lead-soldered.

Methods for the determination of lead in biological materials include dithizone colorimetry,[72,73,78] spectrography,[79] polarography,[80] and atomic absorption spectrophotometry.[69,71,81] In addition, many biochemical tests, reviewed by Chisolm,[82] have been developed; these depend on the lead-induced upset in heme synthesis. Among these biochemical tests are determination of coproporphyrin excretion,[83] urinary ALA[26,84] and ALA-D in blood.[85,86] Additional methods, such as cell stippling, porphobilinogen determinations, and examination of intranuclear inclusion bodies have received less acceptance. These biochemical indices are not recommended at this time. They can be sensitive, perhaps too sensitive, but they are not specific for lead, and are judged to be less useful than blood and urinary lead determinations for estimating the absorption of lead. However, future developments may resolve some of the present objections to the routine use of these indices of alterations of heme synthesis in the assessment of lead absorption.

The dithizone procedure is recommended for analysis of lead in blood and urine. As discussed in the previous section (Basis for Environmental Sampling Method), the method is capable of good results if meticulous attention is given to details, including sources of contamination and loss. Cholak[87] has stated that with careful control the procedure can detect as little as 0.5 μg, with a precision of + 0.5 μg, and that, with modifications, as little as 0.2 + 0.1 μg can be determined. The recommended method as described by Keenan et al.[72] is given in Appendix II. Bismuth is a possible, but uncommon, interfering substance, which can be removed by extraction.

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VII. APPENDIX I

METHOD FOR SAMPLING OF LEAD IN AIR

Lead dust or fume is collected on 0.45 μ cellulose membrane filters mounted in either 2- or 3-piece filter cassettes. Air is drawn through the filter by means of a pump at a rate of 2 liters a minute (not less than 1 nor more than 4 liters per minute). A minimum sample of 100 liters shall be collected. Larger sample volumes are encouraged provided the filters do not become loaded with dust to the point that loose material would fall off or the filter would become clogged.

With each group of samples, one filter, labeled as a blank, shall be submitted; no air shall be drawn through this filter.

The sample cassettes, if shipped, must be packed in a suitable container to prevent damage in transit. Loss of sample shall be prevented; loss of loose deposits on the filter can be prevented by mounting a clean filter in the cassette on top of the sample filter.

Ash the filter and analyze for lead as described in Appendix II.

Other collection methods shown to be equivalent may be used.

VIII. APPENDIX II.

.DITHIZONE METHOD OF ANALYSIS OF LEAD IN AIR AND BIOLOGIC SAMPLES*

The following directions for analysis of lead are taken from the first part of the report, "The 'USPHS' Method for Determining Lead in Air and in Biological Materials" by Keenan, Byers, Saltzman, and Hyslop.[72] Additional information on the reproducibility and accuracy of the method is given in other portions of the report.

REAGENTS

Analytical grade reagents are used. Purification is essential when analyzing biological tissues and fluids because of the very low levels of lead in these materials; purification of reagents may not be required for air samples containing quantities of lead sufficiently greater than that present in the reagent blank. A reagent blank sample is carried through the entire procedure with each set of unknown samples (air, biological, or other type) and its analyzed lead content is subtracted from each analytical result to calculate the net quantity of lead in each unknown sample.

A boiling rod is used to prevent bumping in the flasks when distilling reagents. This is prepared by cutting 3 or 4 mm O.D. glass tubing to a length which is one cm greater than the height of the flask. The tubing is sealed at a spot about one cm above the bottom end which is fire-polished but left open. Before each use, the liquid is shaken out of

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*Alternite methods for analyzing for lead in air (method 5341) and in blood (method P & CAm 262) are given in the NIOSH manual of analytical methods, 2nd Edition 1977 DHEW (NIOSH) Publications No-77-157A and 157B. Available from the Government Printing office, Washington, D.C.

the bottom section and the rod inserted in the flask. As the flask is heated a steady stream of air and vapor bubbles issues from the open space, thus providing nuclei for smooth boiling.

Double-distilled Water - To distilled water in an all borosilicate-glass still add a crystal each of potassium permanganate and barium hydroxide and redistill. Use for reagent and biological sample solutions unless tests indicate that single-distilled water is satisfactory; single-distilled water is usually adequate for determinations on air samples.

Nitric Acid, Concentrated - Redistill in an all borosilicate-glass still the ACS reagent grade acid, 69.0% minimum, specific gravity 1.42. Use an electric heating jacket on the boiling flask to minimize danger of its breakage, and a boiling rod to prevent bumping, which otherwise would be severe. Discard the first 50 ml of distillate; this may be combined with the acid allowed to remain in the flask at the end of the distillation and used for washing glassware. The reagent is conveniently dispensed from a small automatic burette. No grease should be used on the stopcock.

Nitric Acid, 1:99 - Dilute 10 ml of the redistilled, concentrated acid to one liter with doubled-distilled water.

Ammonium Hydroxide, Concentrated - Distill in an all borosilicate-glass still 3 liters of the ACS reagent grade, 28.0% minimum specific gravity 0.8957 at 60 F, into 1.5 liters of double-distilled water,

contained in a 2-liter reagent bottle which is chilled in an ice bath. Continue the distillation until the bottle is filled up to the previously marked 2-liter level. Submerge the condenser tube deeply in the water in the receiver, but withdraw it before discontinuing the heat to avoid siphoning back of distillate. This reagent may be prepared more conveniently from tank ammonia, using a small wash bottle to scrub the gas and a sintered glass delivery tube which extends to the bottom of the reagent bottle. The ammonia gas is absorbed in double-distilled water until the solution reaches the desired specific gravity.

Chloroform - Use a brand with a statement on the label that the chloroform passes the American Chemical Society test for suitability for use in dithizone procedures. In addition, each batch of chloroform should be purchased in glass containers only and should be tested as follows in the laboratory to make sure that it is satisfactory for preparing the dithizone solutions: add a minute quantity of dithizone to a portion of the chloroform in a test tube, shake gently, then stopper with a cork. The faint green color should be stable for one day. Our experience has indicated that the procedures for reclaiming used chloroform are tedious, time-consuming, sometimes unsuccessful, and no longer warranted in view of the commercial availability of acceptable reagent grades.

Extraction Dithizone - Dissolve 16 mg of diphenylthiocarbazone (dithizone), Eastman Kodak Co. No. 3092, or equivalent, in one liter of chloroform. Store in a brown bottle in the refrigerator.

Standard Dithizone - Dissolve 8 mg of diphenythiocarbazone in one liter of chloroform. Store in a brown bottle in the refrigerator but allow to warm to room temperature before using. Age for at least one day, then standardize as described in the procedure. Restandardize every few months.

Sodium Citrate - Dissolve 125 g of the 2 $Na_3C_6H_5O_7 \cdot 11\ H_2O$ salt in sufficient distilled water to provide a solution nearly 500 ml in volume. Adjust the pH to 9-10, using a very small quantity of phenol red indicator solution (strong red color) and fresh, pHydrion test paper to check the pH. Extract in a large separatory funnel with a 100 mg per liter solution of dithizone and finally with the extraction dithizone reagent until a green extract is obtained with the latter reagent. Add a small volume of lead-free citric acid until an orange color (pH 7) appears. Extract the excess dithizone repeatedly with chloroform until a colorless extract is obtained. Remove the last traces of chloroform.

Hydroxylamine Hydrochloride - Dissolve 20 g of the salt in distilled water to provide a volume of 65 ml. Add a few drops of m-cresol purple indicator, then add ammonia until the indicator turns yellow (pH 3). Add a sufficient quantity of a 4% solution of sodium diethyldithiocarbamate to combine with metallic impurities, then mix. After a few minutes extract repeatedly with chloroform until the excess carbamate reagent has been removed, as indicated by the absence of a yellow color in the final chloroform extract tested with a dilute copper solution.

To the aqueous solution of the hydroxylamine hydrochloride add redistilled, 6N hydrochloric acid until the indicator turns pink, and adjust the volume to 100 ml with double-distilled water.

Potassium Cyanide - (Danger! Highly poisonous!!) To 50 g of potassium cyanide in a beaker, add sufficient distilled water to make a sludge. Transfer the sludge to a separatory funnel previously marked to show 100-ml volume. Add a small amount of distilled water to the beaker and warm. (Potassium cyanide cools the solution as it dissolves, thus retarding the solution process.) Add this warm water to the separatory funnel but do not permit contents to exceed the 100-ml mark. Shake, then let stand until the contents come to room temperature. A practically saturated solution results.

Extract the lead by shaking repeatedly with portions of the extraction dithizone solution until the lead has been removed. Part of the dithizone dissolves in the aqueous phase but enough remains in the chloroform to color it. A green extract indicates that all the lead has been completely extracted. Most of the dithizone in the aqueous phase is then removed by repeated extractions with pure chloroform. Dilute the concentrated solution of potassium cyanide with double-distilled water to 500 ml. It should not be necessary to filter the solution, if the directions are followed precisely. Extraction is carried out before dilution because the higher pH of the dilute solution is less favorable.

(NOTE: A colorless solution usually results if above directions are followed. Occasionally aging results in a brown color or precipitate due to polymerization of hydrogen cyanide. This does not interfere with use of the reagent if it is carefully decanted. Old potassium cyanide reagent may lose enough strength to cause insufficient complexing of large amounts of zinc.)

Ammonia-cyanide Mixture - Mix 200 ml of the purified 10% potassium cyanide reagent with 150 ml of distilled ammonium hydroxide (specific gravity 0.9, corresponding to 28.4% NH_3) and dilute to one liter with double-distilled water. If the measured specific gravity of the ammonia is not 0.9, use the equivalent volume as calculated from a table of specific gravity vs. percentage ammonia.

Standard Lead Solution - Dissolve 1.5984 g of pure lead nitrate in one liter of 1:99 nitric acid to provide a strong stock solution containing one mg Pb per ml. Pipet exactly 20 ml into a 500-ml volumetric flask and make to mark with 1:99 nitric acid to give a dilute stock solution containing 40 µg Pb per ml. (A standard lead solution, 10 µg Pb/ml, was stable in 1:99 nitric acid for three years.) Prepare a working solution, containing 2 µg Pb per ml, just before it is needed by pipetting 5 ml of the dilute stock solution into a 100-ml volumetric flask and making to mark with 1:99 nitric acid.

Phenol Red - 0.1% aqueous solution.

Ashing Aid Acid - Dissolve 25 g potassium sulfate in sufficient redistilled concentrated nitric acid to make 100 ml.

White Petrolatum - Supplied in a glass jar, for greasing stopcocks. To check on the purity, put a pinch of this petrolatum in a beaker, add a few milliliters of the standard dithizone and swirl. If the dithizone is no longer green after a few minutes, the material is unsatisfactory for greasing stopcocks.

APPARATUS

A Beckman Model DU Spectrophotometer has been used in this laboratory since this instrument became available in the 1940s. However, the Beckman Model B and the Bausch and Lomb Spectronic 20 have been shown to give comparable results for blood lead determinations, provided that appropriate standardizations are conducted with each instrument. Other laboratories, whose results are reported in this paper, have presumably used a diversity of available photometers and spectrophotometers. In our laboratory, 22 x 175 mm matched test tubes are used in most spectrophotometric procedures employing the Model DU, which is fitted with a tube holder which does not interfere with the use of the instrument with regular cells. These same tubes are used in the Model B fitted with a test tube adaptor. A 3/4-inch tube, supplied by the manufacturer, is used in the Bausch and Lomb Spectronic 20.

Borosilicate glassware is used throughout the procedures (except for vacutainers used for blood sampling). Ashing is performed in 125- or 250-ml Phillips beakers. Automatic burettes are used for the addition of most reagents. The extractions are conducted in the Squibb-type, 125-ml separatory funnels supported in electrically operated shakers provided with timer switches. The stopcocks of the separatory funnels

are greased with white petrolatum (purchased in a glass jar rather than in a metal can or tube) unless Teflon stopcocks, which require no grease, are used. All glassware should be reserved for trace analysis only to avoid possible gross contamination.

Soak all ashing beakers in a detergent solution (Alconox or Duponol is suitable) immediately after each usage to prevent any material from drying on the surfaces. Rinse 8-10 times with hot water and store in a dust-proof drawer or cabinet until needed. Use the following acid cleaning, lead-freeing techniques immediately before the next use of the glassware: Rinse the ashing beakers with a saturated solution of sodium dichromate in concentrated sulfuric acid. Leave a 1-2 ml portion in the beaker or flask (proportionally less in a small volumetric flask!). Add about 5-10 ml of warm tap water and allow the hot solution to flow over all inner surfaces to remove the last traces of grease. Rinse with three or four portions of cold tap water. Rinse with one portion of either concentrated or 1:1 nitric acid, as preferred. (This wash nitric acid may be used repeatedly until it loses its strength.) Then rinse successively with three or four portions each of tap water, distilled and double-distilled water. Set the beakers upright on the bench and cover with a clean dust-case or a large piece of filter paper (or otherwise protect from dust). Under no circumstances is glassware turned upside down to drain on a towel or cheesecloth placed on a laboratory bench. Use an oven operating at 105 C if dry glassware is required.

Separatory funnels are rinsed with tap water immediately after use. If a high lead sample was present or if a visible precipitate remains on the inside, it is rinsed with a small portion of 1:1 wash nitric acid (which is discarded), followed by tap water. The stoppered funnels are stored in double-deck racks. Immediately before use, stopcocks are regreased if necessary. Then the funnels are rinsed with wash acid, four times with tap water, and four times with distilled water. Each rinse is accomplished by shaking with the stopper, then draining through the stopcock with two or three turns.

Spectrophotometer tubes are rinsed four times each with tap and distilled water immediately after use. They are placed upright in a large beaker and dried in an oven at 105 C, then stored under a dust-cover. Occasionally they are cleaned with dichromate-sulfuric acid and nitric acid as described above.

(NOTE: With this method of cleaning glassware we have never encountered cross-contamination from chromium, lead, or from any other trace element being determined routinely in this laboratory.)

ANALYTICAL PROCEDURE

1. Warm the sample ash (prepared as described in the following sections) with 2 ml of concentrated nitric acid for a few minutes, then add 25 ml of distilled water, heating on the hotplate until a clear solution is obtained.

2. Cool to room temperature. Add to the solution in the beaker one ml of hydroxylamine hydrochloride, 4 ml of sodium citrate (10 ml is required for a urine sample), one drop of phenol red indicator, and titrate to a strong red color with concentrated ammonia reagent. Add a few drops excess of ammonia to make sure that the pH is between 9 and 10, using fresh pHydrion test paper to check the pH.

(NOTE: Phenol red has a weak orange-red color in strong acid, yellow in weak acid, and a red color in alkaline solution. Do not mistake the

first color for that produced in alkaline medium!)

3. Transfer the sample quantitatively with double-distilled water rinsings to a 125-ml Squibb separatory funnel containing 5 ml of the potassium cyanide reagent.

4. Add 5 ml of the extraction dithizone and shake two minutes, after releasing the initial pressure by momentarily opening the stopcock of the inverted separatory funnel. Allow the chloroform layer to settle.

5. Draw off most of the extraction dithizone into a second funnel containing exactly 30 ml of 1:99 nitric acid.

6. Add a second 5-ml portion of extraction dithizone to the first funnel and shake as before. Allow the layers to separate and combine the extracts in the second funnel. Continue this process with fresh portions of extraction dithizone until the reagent remains green. A rough estimate of the lead present in the sample may be made on the basis of 20 μg for each cherry-red 5-ml extract portion.

7. Shake the second funnel for two minutes to transfer the lead to the 1:99 nitric acid layer. Allow the layers to separate. Discard the chloroform layer.

8. Shake the nitric acid solution with approximately 5 ml of reagent chloroform and let settle. Drain the settled chloroform through the stopcock bore as completely as possible without loss of the aqueous layer. Evaporate the last drop of chloroform clinging to the upper surface of the liquid.

(NOTE 1: Start a zero lead standard at the beginning of this step by placing 30 ml of 1:99 nitric acid in a separatory funnel. This zero lead standard will be used to set the spectrophotometer at zero absorbance for

each series of samples being analyzed.)

(NOTE 2: If the quantity of lead estimated for any sample exceeds the 25 µg range of the colorimetric determination, pipet an appropriate aliquot of the nitric acid solution at the end of step 7 into a clean separatory funnel containing 5 ml 1:99 nitric acid to minimize errors caused by possible leakage of the stopcock, add sufficient additional 1:99 nitric acid to make 30 ml total volume, and continue with step 8.)

(NOTE 3: Start lead standards at this point if required. Add 5-ml portions of 1:99 nitric acid to each of four separatory funnels, then 2.5, 5.0, 7.5, and 12.5 ml of dilute standard lead solution (2 µg Pb/ml) from a burette, respectively to the separatory funnels, finally add the proper quantity of 1:99 nitric acid to make total volume 30 ml in each. Continue with step 8.)

9. Add 6.0 ml of the ammonia-cyanide mixture, <u>exactly</u> 15.0 ml of the standard dithizone, and shake two minutes. Allow the layers to separate. Drain the chloroform layer containing the lead dithizonate into a clean, dry test tube, and cork the tube immediately.

10. Decant this solution carefully into a dry photometer tube leaving the water behind. If any water spots are visible in the optical light path, transfer again to another photometer tube.

11. Set the spectrophotometer at a wavelength of 510 nm.

12. Set the instrument at zero absorbance using the zero lead standard solution.

13. Read the absorbances of the samples and of the reagent blank.

14. Calculate the lead content of each by multiplying its absorbance by the standardization factor (which is the slope of the standardization plot in micrograms of lead per unit of absorbance.) Subtract the blank value from the gross lead content of each sample to obtain the net amount of lead expressed in micrograms.

SPECIAL MATERIALS FOR BLOOD SAMPLING

1. Vacutainers, Becton-Dickinson, No. 3208, 20-ml or 10-ml, complete with stoppers are used for blood sampling. The vacutainers are used repeatedly and are lead-freed by the technique described previously. Blood is removed from the vacutainers and the stoppers, after each use, by soaking in cold tap water. When no further visible trace of blood remains on these items, they are soaked overnight in the detergent solution. They are then rinsed repeatedly with hot tap water to remove alkaline materials. The vacutainers are then subjected to the chromic and nitric acid cleaning procedures. The stoppers are soaked for 20- to 30-minute periods, three times, with single distilled water and finally three times with double distilled water. The lead-freed vacutainers are dried at 105 C, fitted with clean stoppers, and stored in a drawer reserved for them. Layers of cheesecloth are placed between the separate layers of vacutainers and the drawer is sealed with masking tape to prevent the admittance of any dust. They are evacuated just before shipment to the field. A vacuum tester is used both in the laboratory and field to test for loss of vacuum, which usually will not occur until stoppers have been used several times.

2. Vacuum Tester, High Frequency, Fisher Cat. No. 1-179, or equivalent.

3. Needles, Becton-Dickinson, Gauge 20, one and one-half inches in length, stainless steel, B-D No. 3200 N. As these needles are used repeatedly, check the tips for burrs by drawing them across the thumb nail. When burrs develop either discard the needles or file off the burrs. After filing, they must be recleaned. Vacutainer needles are soaked in a dilute detergent solution. A Becton-Dickinson Needle Cleaner, No. 3200 C, is used to force detergent solution and subsequent rinse water through the needles. Needles are subjected to thorough rinsing with distilled water. They are then placed in steritubes and either autoclaved or heated for two hours in a drying oven operating at 180 C. The steritubes are then fitted with rubber caps.

4. Steritubes, Becton-Dickinson, No. 3200 D, with rubber caps.

5. Stillets for No. 3200 N needles, 20 Gauge, two and seven-eighths inches long.

(These BD items are available from the Becton-Dickinson Company, Rutherford, New Jersey.)

COLLECTING AND ASHING BLOOD SAMPLES

Collect a 10-ml sample of whole blood using a lead-free vacutainer and a sterilized, stainless steel needle. In the laboratory, transfer the sample to a weighed, lead-free, 125-ml borosilicate Phillips beaker. No aliquoting of the blood is permissible, as most of the lead is present in the clot. Determine the weight of the blood sample to the nearest 0.01 gram, weighing rapidly to minimize evaporation. Add 2 ml of ashing aid acid reagent. Add 7 ml of concentrated nitric acid. (This ashing system

permits the analyst to handle a large number of samples at a time as the blood clot breaks up readily and smoothly without bumping and without requiring the constant attention of the analyst.) Place the samples on a hotplate operating about 130 C and evaporate just to dryness. After the water is driven off in the initial evaporation to dryness, keep the beaker covered with a lead-free watchglass to increase the reflux action of the concentrated acid. This serves to wash solids down from the sides to the hotter zone at the bottom, and also reduces the amount of acid needed. Cool the beaker briefly and then add successive portions of the nitric acid ranging from 2 ml down to 0.5 ml as the ashing proceeds. Do not remove the watchglass at any time but merely slide it back sufficiently to facilitate each new addition of the acid. Each time, as soon as the residue becomes light colored, heat on a 400 C hotplate just long enough to blacken the residue, then remove and cool the sample. Throughout the remainder of the ashing procedure, alternately heat the sample with a few drops of nitric acid on the 130 C hotplate and bake the residue for the few minutes required to darken it on the 400 C hotplate. Finally, the residue will remain pale yellow or light brown (due to iron content) after heating for 5-10 minutes at the high temperature. Avoid excess baking at this stage as the ash will become decomposed to a difficultly soluble form. It is now ready for solution and analysis. Report results as milligrams of lead per 100 grams of whole blood.

COLLECTING AND ASHING URINE SAMPLES

Use lead-free, narrow-mouthed, reagent-type, borosilicate, 250-ml bottles provided with standard taper glass stoppers to collect grab samples of

urine. Add 2.0 ml of a 37% formalin solution as a preservative, shaking the bottle 10-12 times after the contribution of the urine to mix the specimen with the formalin thoroughly.

Alternatively, urine specimens may be collected in 125-ml polyethylene bottles containing as a preservative 100-200 mg of EDTA (acid form) per bottle. This is convenient and economical for shipping samples considerable distances.

If the urine sample is clear and only one or two days old, measure a 50 ml portion into a graduated cylinder. However, if the sample is older, much of the lead may be in a sediment or on the walls of the bottle and must be dissolved before aliquoting. Transfer the entire specimen to a glass-stoppered graduated cylinder, record the volume, rinse the sample bottle with three small portions of concentrated nitric acid and add these rinsings to the cylinder. Mix thoroughly (Caution! Old samples may foam over.) Note the total volume and remove an aliquot equivalent to 50 ml of urine for analysis. Transfer the aliquot portion to a lead-free, 250-ml borosilicate Phillips beaker and add 5 ml of redistilled concentrated nitric acid. Evaporate just to dryness on a hotplate operating at about 130 C. Cool, add sufficient nitric acid to moisten the residue and cover the beaker with a lead-free watchglass. Heat on the 130 C hotplate and then alternately bake for a few minutes and digest with minimal amounts of nitric acid (as described in the ashing method for blood) until a white residue remains after the final heating for 5-10 minutes at the high temperature. The sample is now ready for solution and analysis. Report results as milligrams of lead per liter of urine.

PROCEDURE FOR AIR SAMPLES

It is convenient to wash out samples in electrostatic precipitator tubes with redistilled ethanol, using a special policeman made with a rubber disc cut to fit the tube like a piston, and transferring the sample through a short stem funnel into a 250-ml Phillips beaker; gently evaporate just to dryness. (Ethanol is helpful in removing greasy deposits on the walls of the precipitator tube. Some chemists may prefer hot 1 to 5% nitric acid to transfer the sample.) Transfer impinger samples or membrane filter samples to Phillips beakers. If little ash is expected (usually for impinger or membrane filter samples), add 2 ml of ashing aid acid reagent. (The presence of this salt will prevent loss of lead by glazing onto the surface of the beaker during ashing.) Otherwise add 1-2 ml nitric acid. Evaporate to dryness. Continue ashing with nitric acid at a moderate heat until organics are destroyed.

Dissolve the ash in 2 ml of concentrated nitric acid and distilled water and then transfer quantitatively to a 100-ml volumetric flask and make to mark. Pipet a suitable aliquot into a separatory funnel, containing about 5 ml of double-distilled water, add sufficient additional double-distilled water to make the total volume about 25 ml, and apply the Analytical Procedure, starting with step 2. In step 3, as the sample is already in a separatory funnel, merely add the cyanide. The amount of lead present in the aliquot may be estimated as described in step 6. If it is less than a few micrograms, an additional aliquot may be added to the same funnel, and the pH readjusted with ammonia. The extraction is then continued, and extracts combined with those collected previously in the second funnel. If the estimated amount

of lead exceeds the range of the method (25 micrograms), take an aliquot as described in Note 2, step 8.

When calculating the results, make allowance for the total number of aliquots. If convenient, aliquot the reagent blank in the same manner so that the correction represents the same amounts of ashing and extraction reagents as are present in the sample. However, the blank correction is usually small for air samples. Report results as milligrams of lead per cubic meter of air.

IX. _ APPENDIX III

MATERIAL SAFETY DATA SHEET

The following items of information which are applicable to a specific product or material containing lead shall be provided in the appropriate section of the Material Safety Data Sheet or other approved form. If a specific item of information is inapplicable (i.e. flash point) initials "n.a." (not applicable) should be inserted.

(i) The product designation in the upper left hand corner of both front and back to facilitate filing and retrieval. Print in upper case letters in as large print as possible.

(ii) Section I. Name and Source

(A) The name, address, and telephone number of the manufacturer or supplier of the product.

(B) The trade name and synonyms for a mixture of chemicals, a basic structural material, or for a process material; and the trade name and synonyms, chemical name and synonyms, chemical family, and formula for a single chemical.

(iii) Section II. Hazardous Ingredients

(A) Chemical or widely recognized common name of all hazardous ingredients.

(B) The approximate percentage by weight or volume (indicate basis) which each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range of maximum amount, i.e., 10-20% V; 10% max. W.

(C) Basis for toxicity for each hazardous material such as established OSHA standard in appropriate units and/or LD_{50}, showing amount and mode of exposure and species or LC_{50} showing concentration and species.

(iv) Section III. Physical Data

(A) Physical properties of the total product including boiling point and melting point in degrees Fahrenheit; vapor pressure, in millimeters of mercury, vapor density of gas or vapor (air = 1), solubility in water, in parts per hundred parts of water by weight; specific gravity (water = 1); volatility, indicate if by weight or volume, at 70° Fahrenheit; evaporation rate for liquids (indicate whether butyl acetate or ether = 1); and appearance and odor.

(v) Section IV. Fire and Explosion Hazard Data

(A) Fire and explosion hazard data about a single chemical or a mixture of chemicals, including flash point, in degrees Fahrenheit; flammable limits, in percent by volume in air; suitable extinguishing media or agents; special fire fighting procedures; and unusual fire and explosion hazard information.

(vi) Section V. Health Hazard Data

(A) Toxic level for total compound or mixture, relevant symptoms of exposure, skin and eye irritation properties, principal routes of absorption, effects of chronic (long-term) exposure, and emergency and first aid procedures.

(vii) Section VI. Reactivity Data

(A) Chemical stability, incompatibility, hazardous decomposition products, and hazardous polymerization.

(viii) Section VII. Spill or Leak Procedures

(A) Detailed procedures to be followed with emphasis on precautions to be taken in cleaning up and safe disposal of materials leaked or spilled. This includes proper labeling and disposal of containers containing residues,

contaminated absorbants, etc.

(ix) Section VIII. Special Protection Information.

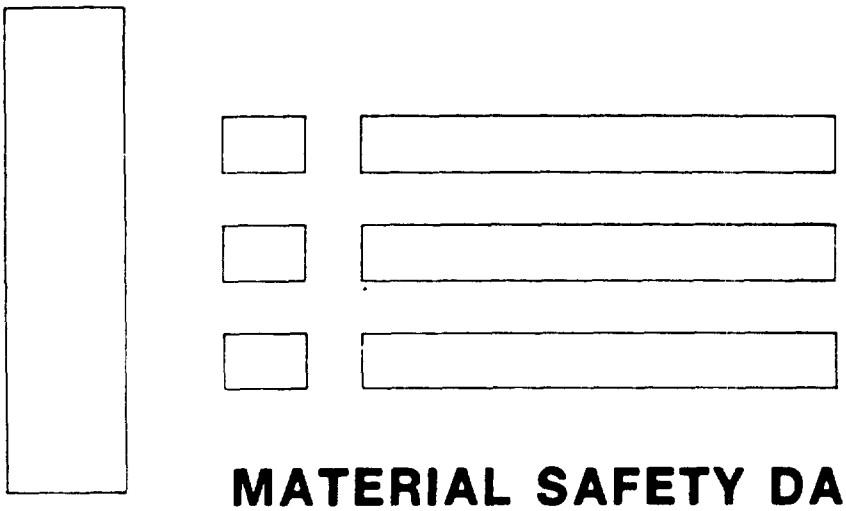
(A) Requirements for personal protective equipment, such as respirators, eye protection and protective clothing, and ventilation such as local exhaust (at site of product use or application), general, or other special types.

(x) Section IX. Special Precautions.

(A) Any other general precautionary information such as personal protective equipment for exposure to the thermal decomposition products listed in Section VI, and to particulates formed by abrading a dry coating, such as by a power sanding disc.

(xi) The signature of the responsible person filling out the data sheet, his address, and the date on which it is filled out.

(xii) The NFPA 704M numerical hazard ratings as defined in section (c) (5) following. The entry shall be made immediately to the right of the heading "Material Safety Data Sheet" at the top of the page and within a diamond symbol preprinted on the forms.



MATERIAL SAFETY DATA SHEET

I PRODUCT IDENTIFICATION	
MANUFACTURER'S NAME	REGULAR TELEPHONE NO EMERGENCY TELEPHONE NO
ADDRESS	
TRADE NAME	
SYNONYMS	

II HAZARDOUS INGREDIENTS		
MATERIAL OR COMPONENT	%	HAZARD DATA

III PHYSICAL DATA			
BOILING POINT 760 MM HG		MELTING POINT	
SPECIFIC GRAVITY (H_2O = 1)		VAPOR PRESSURE	
VAPOR DENSITY (AIR = 1)		SOLUBILITY IN H_2O, % BY WT	
% VOLATILES BY VOL		EVAPORATION RATE (BUTYL ACETATE = 1)	
APPEARANCE AND ODOR			

IV FIRE AND EXPLOSION DATA

FLASH POINT (TEST METHOD)		AUTOIGNITION TEMPERATURE	
FLAMMABLE LIMITS IN AIR, % BY VOL	LOWER		UPPER
EXTINGUISHING MEDIA			
SPECIAL FIRE FIGHTING PROCEDURES			
UNUSUAL FIRE AND EXPLOSION HAZARD			

V HEALTH HAZARD INFORMATION

HEALTH HAZARD DATA

ROUTES OF EXPOSURE

INHALATION

SKIN CONTACT

SKIN ABSORPTION

EYE CONTACT

INGESTION

EFFECTS OF OVEREXPOSURE

ACUTE OVEREXPOSURE

CHRONIC OVEREXPOSURE

EMERGENCY AND FIRST AID PROCEDURES

EYES

SKIN

INHALATION

INGESTION

NOTES TO PHYSICIAN

VI REACTIVITY DATA

CONDITIONS CONTRIBUTING TO INSTABILITY

INCOMPATIBILITY

HAZARDOUS DECOMPOSITION PRODUCTS

CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION

VII SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

NEUTRALIZING CHEMICALS

WASTE DISPOSAL METHOD

VIII SPECIAL PROTECTION INFORMATION

VENTILATION REQUIREMENTS

SPECIFIC PERSONAL PROTECTIVE EQUIPMENT

RESPIRATORY (SPECIFY IN DETAIL)

EYE

GLOVES

OTHER CLOTHING AND EQUIPMENT

IX SPECIAL PRECAUTIONS

PRECAUTIONARY STATEMENTS

OTHER HANDLING AND STORAGE REQUIREMENTS

PREPARED BY

ADDRESS

DATE

TABLE X-1

Physical Properties of Lead

Property	Value	
Atomic Number	82	
Atomic Weight	207.19	
Thermal Conductivity	0.346 watts/cm C	(25 C)
Density	11.344 g/ml	(16 C)
Melting Point	327.5 C	
Boiling Point	1744 C	
Electrical Resistivity	20.6 μohm-cm	(20 C)

Adapted from reference[1]

TABLE X-2

Lead consumption in the United States, by products 1969

(Short tons)

Product	1969
Metal products:	
Ammunition	79,233
Bearing metals	17,406
Brass and bronze	21,512
Cable covering	54,203
Calking lead	44,857
Casting metals	9,918
Collapsible tubes	12,484
Foil	5,881
Pipes, traps, and bends	19,407
Sheet lead	25,818
Solder	72,626
Storage batteries:	
Battery grids, posts, etc.	280,386
Battery oxides	302,160
Terne metal	1,583
Type metal	25,660
Total	973,134
Pigments:	
White lead	6,617
Red lead and litharge	79,898
Pigment colors	14,670
Other	1,201
Total	102,386
Chemicals:	
Gasoline antiknock additives	271,128
Miscellaneous chemicals	602
Total	271,730
Miscellaneous uses:	
Annealing	4,252
Galvanizing	1,797
Lead plating	406
Weights and ballast	17,366
Total	23,821
Other, unclassified	18,287
Grand total	1,389,358

Adapted from Reference 2

TABLE X-3

Potential Occupational Exposures to Inorganic Lead

Babbitters
Battery makers
Bookbinders
Bottle cap makers
Brass founders
Brass polishers
Braziers
Brick burners
Brick makers
Bronzers
Brush makers
Cable makers
Cable splicers
Canners
Cartridge makers
Ceramic makers
Chemical equipment makers
Chippers
Cutlery makers
Demolition workers
Dental technicians
Diamond polishers
Dye makers
Electronic device makers
Electroplaters
Electrotypers
Emery wheel makers
Enamel burners
Enamelers
Enamel makers
Farmers
File cutters
Filers
Flower makers, artificial
Foundry molders
Galvanizers
Glass makers
Glass polishers
Gold refiners
Gun barrel browners
Incandescent lamp makers
Insecticide makers
Insecticide users
Japan makers
Japanners
Jewelers
Junk metal refiners
Lacquer makers
Lead burners
Lead counterweight makers
Lead flooring makers
Lead foil makers
Lead mill workers
Lead miners
Lead pipe makers
Lead salt makers
Lead shield makers
Lead smelters
Lead stearate makers
Lead workers
Linoleum makers
Linotypers
Lithographers
Match makers
Metal burners
Metal cutters
Metal grinders
Metal miners
Metal polishers
Metal refiners
Mirror silverers
Motor fuel blenders
Musical instrument makers
Painters
Paint makers
Paint pigment makers
Patent leather makers
Pearl makers, imitation
Pipe fitters
Plastic workers
Plumbers
Pottery glaze mixers
Pottery workers
Putty makers
Riveters
Roofers
Rubber buffers
Rubber makers
Scrap metal workers
Sheet metal workers
Shellac makers
Ship dismantlers
Shoe stainers
Shot makers
Solderers
Solder makers
Steel engravers
Stereotypers
Tannery workers
Temperers
Tetraethyl lead makers
Tetramethyl lead makers
Textile makers
Tile makers
Tin foil makers
Tinners
Type founders
Typesetters
Varnish makers
Wallpaper printers
Welders
Zinc mill workers
Zinc smelter chargers

From reference 3

Operation	General Exposure Incidence of Plumbism
Metalizing	High
Paint spraying: red lead	High
Brush painting: red lead	Some
Paint sanding, scraping	High
Leaded iron pouring	High
Bearing bronze pouring	Some
Bearing bronze grinding	Low
Storage-battery manufacturing:	
Mixing	Some
Pasting	Some
Grouping	Some
Separating	Low
Casting	Low
Lead smelting, refining	Some
Lead burning	Some
Homogenizing	Some
Painted-steel burning	Some
Lead powder mixing	Some
Lead sanding, grinding	Some
Paint mixing	Low
Painting, N.O.C.	Low
Paint spraying: chrome yellow	Low
Wire patenting	Low
Steel tempering	Low
Bronze pouring	Low
Bronze grinding	Low
Lead casting	Low
Printing:	
Stereotyping	Low
Linotyping	None
Soldering, tinning	Low
Lead sawing	Low
Lead glass working	Low
Gasoline-tank cleaning	Low

TABLE X-4

from Operations Utilizing Lead

Average Lead Concentrations Found			
Air (mg/m3)		Urine (mg/1)	
Avg	Max	Avg	Max
1.8	3.5		
		0.26	0.35
0.32		0.30	0.48
19.5			
1.86	3.4	0.54	0.82
0.84		0.33	
0.73	3.8	0.70	1.00
0.75	2.1	0.26	0.48
0.50	4.0	0.22	0.68
0.15	0.41	0.15	0.27
0.26	0.65	0.19	0.31
0.35	1.45	0.35	0.88
0.57	1.5	0.26	0.37
3.0			
		0.41	0.50
2.2	10.2	0.22	0.32
4.2	7.4	0.26	
1.75	5.8	0.17	0.29
		0.09	0.16
3.9		0.10	
0.29	0.60	0.12	0.21
0.13	0.22	0.10	0.21
0.34	1.56	0.20	0.34
0.47	1.24	0.17	0.34
0.12	0.35	0.14	0.37
0.26	0.51	0.15	0.22
0.07	0.24	0.08	0.14
0.25	0.62	0.15	0.23
0.25			
0.01	0.02	0.05	0.10
		0.07	0.14

TABLE X-5

Biochemical Values at Two Airborne Levels of Lead

Air Pb conc. mg/m	Biochemical Test, mean (and 95% confidence limits)			
	Blood Pb mg/100 ml	Urine Pb mg/liter	Urine Coproporphyrin (Donath)	Urine ALA* mg/100 ml
0.20	0.070 (0.048-0.092)	0.143 (0.056-0.230)	4.2 (2.4-6.0)	1.8 (0.3-3.3)
0.15	0.060 (0.038-0.082)	0.118 (0.031-0.205)	3.6 (1.8-5.4)	1.4 (0.1-2.9)

* ALA values were determined by a method which probably gives higher values than do other methods, thus a high "normal" value.

From Williams, King and Walford [47]

TABLE X-6

Representative Lead Exposures in the Printing Industry

Location	Nature of Operations or Exposure	Lead Concentration in mg/m^3			Remarks
		Max.	Min.	Ave.	
Linotype Room	Lead concentration about 12" above lead pot of one of centrally located machines	0.027	0.007	0.014	Pot temperature ranged from 515° to 550° F.
	Exposure of machine operators	0.020	0.006	0.012	
Monotype Room	Lead concentration about 12" above lead pot of one of centrally located machines	0.570	0.056	0.163	Pot temperature ranged from 660° to 835° F.
	Exposure of machine operators	0.096	0.027	0.056	
Remelt Room	Average room concentration	0.158	0.004	0.041	Melt kettles enclosed are exhaust ventilated
	Workers' exposure while filling molds	0.132	0.035	0.073	Worker's face about 18 to 24[11] above molds while being poured. Lead temperature 600° to 700° F.
	Room concentration while drossing kettles and while removing copper plates from electrotype	0.257	0.149	0.196	Several kettles drossed during sample but only one kettle door open at a time
Composing Room	Average room concentration	0.118	0.016	0.062	
Stereotype Room	Concentration at or near the breathing level of workers operating lead pots, pouring molds, etc.	0.026	0.003	0.008	Pot temperature ranged from 550° to 600° F.
	Exposure of operators of trimming and finishing machines such as saws, bevelers, planers and routers	0.442	0.002	0.104	

Adapted from reference [53]

TABLE X-7

REPRESENTATIVE LEAD EXPOSURE IN PRINTING OPERATIONS

Description of Exposure	No. Of Samples	Range mg/m^3	Mean mg/m^3
Lead Concentrations over Linotype Melting Pots	9	< 0.01 - 0.054	0.029
Concentrations While Cleaning Linotype Plungers	6	0.06 - 2.8	0.783
Concentrations Around Metal Pots While Removing Dross	9	1.4 - 160.0	29.30
Atmospheric Lead at Breathing Zone of Linotype Operators	17	< 0.01 - 0.049	0.021
Atmospheric Lead in Hand Composing Areas Adjacent to Linotypes	7	< 0.01 - 0.045	0.017
Lead in General Atmosphere of Monotype Rooms	12	< 0.01 - 0.060	0.028
Lead Concentration 6 inches Above Monotype Metal Pots	22	< 0.01 - 10.0	1.070
Lead Concentrations 19 inches Above Monotype Metal Pots	8	< 0.01 - 0.38	0.148
Atmospheric Lead in Vicinity of Unexhausted Remelt Furnace During Various Phases of Operation			
1. Loading & Heating	8	< 0.01 - 0.16	0.052
2. Cleaning & Drossing	7	5.10 - 50.0	15.26
3. Pouring	7	0.094 - 0.78	0.313
Atmospheric Lead in Vicinity of Exhausted Remelt Furnace During Various Phases of Operation			
1. Loading & Heating	2	0.881 - 0.15	0.116
2. Cleaning & Drossing	2	1.8 - 5.3	3.55
3. Pouring	2	0.053 - 0.15	0.102

Sampling - Electrostatic Precipitator
Analysis - Dithizone
Adapted from reference [54]

TABLE X-8

Representative Lead Exposure in the Printing Industry

	Years in Printing	Calculated Exposure mg/m^3	Urine Lead mg/liter
Linotype Operators			
	9	0.03	-
	16	0.03	0.11
	15	0.10	0.04
	6	0.02	-
	20	0.02	0.17
	15	0.02	0.11
	19	0.02	0.17
	38	0.02	-
	12	0.02	-
	22	0.02	-
	11	0.02	-
	40	0.09	0.16
	18	0.02	0.11
	3	0.02	0.32
	8	0.04	0.21
	6	0.02	0.19
	4	0.02	0.24
	15	0.10	0.28
	20	0.10	0.26
Monotype Operators			
	3	0.04	0.03
	10	0.09	0.28
	19	0.06	0.17
	7	0.04	0.10
	17	0.06	0.18
Remelt Men			
	2	0.38	0.17
	7	0.15	0.13
	1	0.04	0.28
	10	0.09	0.06
	3	0.50	-
	5	0.03	-
	9	0.13	0.19

TABLE X-8 Cont.

	Years in Printing
Stereotypers	
	1
	10
	4
	1
Others	
	26
	1
	2
	6
	10

Sampling - Electrostatic Precipitator
Analysis - Dithizone

Adapted from Reference 55

Calculated Exposure mg/m^3	Urine Lead mg/liter
0.09	0.27
0.10	0.17
0.08	0.29
0.10	0.26
0.02	0.23
0.03	0.36
0.07	0.23
0.02	-
0.02	-

TABLE X-9

Representative Mean Lead Exposures and Biologic Lead Levels for Workers in the Storage Battery Industry

Job	Number Workers	Air Lead Concentration, mg/m^3		Blood Lead Concentration, µg/100g Blood		Urine Lead Concentration, µg/Liter	
		Mean	SE	Mean	SE	Mean	SE
Machine pasting	6	0.218	0.025	74.2	4.7	163.8	21.2
Hand pasting	8	0.150	0.029	63.2	9.2	111.3	14.1
Forming	9	0.134	0.013	63.0	2.7	114.0	7.2
Casting	6	0.052	0.003	-	-	87.9	6.8
Plastics department A	5	0.012	0.0008	27.2	1.4	34.5	3.2
Plastics department B	5	0.009	0.0008	29.1	1.6	34.8	2.0

Adapted from reference [47]

TABLE X-10

Average and Median Blood Lead Content in mg/100 g of Blood in Storage-Battery Workers, by Exposure and Duration of Employment.

Duration of Lead Exposure, Years	Air Lead Content, mg/m^3				
	0-0.074	0.075-0.14	0.15-0.29	≥0.3	% >0.15
0-4					
Number	17	16	32	20	
Average	0.0187	0.0316	0.0378	0.0463	59
Median	0.021	0.030	0.038	0.050	
5-9					
Number	10	13	40	24	
Average	0.0278	0.0405	0.0501	0.0505	74
Median	0.033	0.040	0.043	0.050	
10-14					
Number	23	24	30	32	
Average	0.0198	0.0375	0.0502	0.0481	57
Median	0.018	0.038	0.046	0.048	
15+					
Number	44	30	59	45	
Average	0.0293	0.0407	0.0457	0.0493	58
Median	0.023	0.036	0.045	0.045	

Analysis - Dithizone

Adapted from references 4 and 11

TABLE X-11

REPRESENTATIVE LEAD EXPOSURES WHILE PERFORMING

WELDING OPERATIONS UNDER VARIOUS CONDITIONS

Coating	Type weld	Location of sampling probe	Lead	Avg.
POOR VENTILATION†		EXPERIMENTAL AREA	mg/m^3	
Zinc-silicate	Elect. arc	2' directly above welding	15.2	
" "	" "	3' above and 2-1/2 back of welding*	0.86	
" "	" "	3' above and 2' back of welding*	3.27	5.63
" "	" "	3' above and 2' back of welding*	3.65	
" "	" "	Attached to welder's shoulder*	5.16	
Zinc-silicate	Oxy-acetylene	1' above and 1' back of welding*	3.53	
" "	" "	3' above and 2-1/2' back of welding*	1.24	
" "	" "	3' above and 2-1/2 back of welding*	1.56	
" "	" "	3' above and 2' back of welding*	1.80	1.96
" "	" "	3' above and 2' back of welding*	1.80	
" "	" "	3' above and 2' back of welding*	1.76	
" "	" "	3' above and 2' back of welding*	2.00	
Galvanized steel	Elect. arc	2' above and 1' back of welding*	0.40	
" "	" "	2' above welder's face	0.69	
" "	" "	6' above floor, 5' in front of welder	0.35	0.52
" "	" "	Attached to welder's shoulders*	0.64	
Galvanized steel	Oxy-acetylene	2'above and 2' back of welding*	0.66	
" "	" "	3' above and 2-1/2' back of welding*	0.24	
" "	" "	2' above and 1' back of welding*	0.41	0.43
" "	" "	6' above and 5' back of welder	0.30	
" "	" "	3' above and 1' back of welding	0.55	

TABLE X-11 (CONTINUED)

Coating	Type weld	Location of sampling probe	Lead	Avg.
Clean steel	Elect. arc	2' above and 1' back of welding. (Control sample)	0	
" "	Oxy-acetylene	20' from welding enclosure (Room air. Control sample)	0	
" "	Elect. arc	20' from welding enclosure (Room air. Control sample)	0	
GOOD VENTILATION		(BREATHING ZONE SAMPLES)		
Zinc-silicate	Oxy-acetylene cutting	Attached near welder's nose**	0.18	
Zinc-silicate	Electric arc beading	Inserted in welder's hood**	0.08	
Zinc-silicate	Electric arc welding	Inserted in welder's hood**	0.14	
Galvanized steel	Oxy-acetylene cutting	Attached near nose**	0.01	
Galvanized steel	Electric arc welding	Inserted in welder's hood**	0.01	
ROOM AIR SAMPLES		(DOWNWIND FROM WELDER)		
Zinc-silicate	Elect. arc	3' downwind from the welder. 3' from floor	0.81	
" "	" "	3' downwind from the welder. 3' from floor	0.76	0.78
" "	" "	20' downwind from the welder. 3' from floor	0.26	
" "	" "	20' downwind from the welder. 3' from floor	0.24	0.25
" "	" "	20' downwind from the welder. 6' from floor	0.27	
" "	" "	20' downwind from the welder. 6' from floor	0.53	0.40

TABLE X-11 (CONTINUED)

Coating	Type weld	Location of sampling probe	Lead	Avg
OUTDOOR SAMPLES		(10 MPH WIND)		
Zinc-silicate	Elect. arc	Welder sat upwind. Probe inserted in hood.	0.06	
Galvanized steel	Elect. arc	Welder sat upwind. Probe inserted in hood.	0.01	
Galvanized steel	Oxy-acetylene (cutting)	Welder sat upwind. Probe was held 3" from nose.	0.00	

† Samples were not collected inside welder's hoods.
* Sample probe located near welder's face.
** Welder located upwind from welding.

Analysis - Dithizone
Adapted from Reference 56

TABLE X-12

Lead Exposures and Urinary Lead Levels from the Cutting of Painted Structural Steel

Exposures (Breathing Zone)	No.	Exposure mg/m^3
	1	0.18
	2	0.50
	3	2.40
	4	1.70
	Avg.	1.20

Urine-Lead	Respirator	Sp. Gr.	Mg. Lead/Liter Urine	
	Mech. Filter	1.014	0.06	
	Mech. Filter	1.025	0.34	
	Mech. Filter	1.026	0.30	
	Mech. Filter	1.030	0.53	
	Mech. Filter	1.016	0.36	
	Mech. Filter	1.020	0.58	Avg. 0.39
	Mech. Filter	1.034	0.28	
	Mech. Filter	1.025	0.70	
	Mech. Filter	1.031	0.50	
	Mech. Filter	1.020	0.49	
	Mech. Filter	1.030	0.33	
	Mech. Filter	1.020	0.26	
	Canister-Type	1.020	0.26	Avg. 0.25
	Canister-Type	1.030	0.24	

Adapted from Reference 57

TABLE X-13

DISTRIBUTION OF PERSONS IN VARIOUS OCCUPATIONAL GROUPS ACCORDING TO CONCENTRATIONS OF LEAD IN BLOOD-CINCINNATI

Lead in blood, mg/100g	Service station attend-ants 1956	Refinery handlers of gasoline 1956	Park-ing attend-ants 1956	Garage Me-chanics 1956	Drivers of cars		Police			Fire-men 1963	Post-Office Emp. 1963	City Health Dept. Emp. 1963
							Traffic officers		All police*			
					1956	1963	1956	1963	1963			
0-0.009												
0.010-0.019	1	2				1		3	12	18	22	10
0.020-0.029	42	30	1	8	17	4	7	23	78	123	90	24
0.030-0.039	71	46	26	43	19	9	9	9	27	44	24	2
0.040-0.049	14	8	20	72	9		1	4	5	6	2	
0.050-0.059	2			25							1	
0.060-0.069			1	4				1	1		1	
Totals	130	86	48	152	45	14	17	40	123	191	140	36
Mean	0.028	0.027	0.034	0.038	0.033	0.031	0.031	0.030	0.025	0.025	0.023	0.021
Std. Dev.	0.007	0.006	0.006	0.009	0.006	0.006	0.006	0.009	0.007	0.006	0.007	0.005

*Includes traffic officers for 1963.

From reference 58

TABLE X-14

DISTRIBUTION OF PERSONS IN VARIOUS OCCUPATIONAL GROUPS ACCORDING TO CONCENTRATIONS OF LEAD IN URINE-CINCINNATI

Lead in urine, mg/100g	Service station attend-ants 1956	Refinery handlers of gasoline 1956	Park-ing attend-ants 1956	Garage Me-chanics 1956	Drivers of cars		Police			Fire-men 1963	Post-Office Emp. 1963	City Health Dept. Emp. 1963
							Traffic officers		All police*			
					1956	1963	1956	1963	1963			
0-0.009	1	1	1	4	1			2	2			
0.010-0.019		1	4	2	28		9		6	47	49	12
0.020-0.029	74	49	21	39	11	5	5	13	29	71	52	18
0.030-0.039	33	22	12	33	2	4		7	21	36	19	6
0.040-0.049	13	9	7	30	2	4	3	8	30	19	9	1
0.050-0.059	5		2	21		1		2	12	9	1	
0.060-0.069	3	4	1	16				1	7	2		
0.070-0.079				4	1			1	3	1		
0.08-0.12	1			3				3	6			
Totals	130	86	48	152	45	14	17	37	116	185	130	37
Mean	0.027	0.028	0.028	0.040	0.020	0.036	0.023	0.039	0.038	0.027	0.022	0.022
Std. Dev.	0.010	0.013	0.011	0.020	0.011	0.010	0.011	0.020	0.018	0.011	0.009	0.007

*Includes traffic officers for 1963.

From reference 58

XI - Appendix IV

FINAL REPORT

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REVIEW, SUMMARIZATION, AND EVALUATION OF LITERATURE TO SUPPORT THE UPDATE AND REVISION OF CRITERIA DOCUMENTS
INORGANIC LEAD

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Contract No. 210-76-0167
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I. INTRODUCTION

This report presents a review and evaluation of the recent scientific literature relevant to an occupational hazard assessment of inorganic lead. It is intended to provide an update for the existing NIOSH criteria document for inorganic lead by considering the results of published research which have appeared since the preparation of the original document.

In assembling this update report, pertinent new information was sought in the areas of: (a) human and animal toxicity, (b) analytical, and sampling methods, (c) work practices and engineering controls, and (d) miscellaneous aspects regarding biological monitoring and medical surveillance. Identification of relevant articles published since 1972 was accomplished through a search of the scientific literature utilizing both computerized and manual searching of various data systems and published secondary bibliographic sources (see Appendix A).

Environmental pollution by inorganic lead is a widespread problem attributable to various sources. Exposure occurs from dietary contamination, and inhalation of lead-containing automobile emissions, as well as by direct occupational contact. Because of the vast literature concerning the health effects of inorganic lead, it was necessary to restrict much of the discussion in this report to those data which have relevance in establishing damage risk criteria in occupational situations. Selections have been made from the large body of literature on lead poisoning in children in those cases where specific analytical techniques, biological monitoring indices, or unique lead-induced effects can be extrapolated to the overall occupational setting. It should be recognized from the outset, however, that children are

generally regarded as being more susceptible to lead intoxication than adults. Thus, the derivation of safe exposure limits is compounded in difficulty by the inherent variability of dose-response parameters with age.

Several major conferences have been held in recent years which dealt specifically with the health effects of inorganic lead. Among these meetings are the National Conference on Health Effects of Occupational Lead and Arsenic Exposure, Chicago, February 24-25, 1975; International Conference on Heavy Metals in the Environment, Toronto, October 27-31, 1975; Conference on Low Level Lead Toxicity, Raleigh, N.C., October 1-2, 1973 (papers published in Environmental Health Perspectives, Exp. Issue No. 7, 1974); and Conference on Standards for Occupational Lead Exposure, Washington, D. C., February 28, 1974 (proceedings published in Journal of Occupational Medicine, Vol. 17, No. 2, 1975).

II. SAMPLING AND ANALYSIS

A. Presently Recommended Analysis

The NIOSH document [1] specifies methods for sampling and analysis of workplace air and biological indices of inorganic lead poisoning in occupationally exposed workers. It recommends the dithizone colorimetric method for analysis of both air and biological specimens for lead content. The stated limit of detection is 0.2 ± 0.1 μg of lead. Bismuth is the only acknowledged interference, but its presence is rare. The document mentions several alternative methods which were ruled out in favor of the dithizone procedure. Although it recognizes that numerous atomic absorbance spectroscopic methods were available and competitive with the dithizone method, the document concludes that an acceptable standard atomic absorbance format had not been developed and adequately tested.

The document [1] specifies that air samples should be collected by breathing zone samplers. Air samples are to consist of 100 or more liters pumped at a rate of ca. 2 liters per minute (allowed range of 1 to 4 liters per minute) through 0.45 μ cellulose membrane filters.

While the document [1] prefers blood lead concentration as an index of exposure, it accepts urine lead as an alternative (although not quantitatively as good an index). Other biological indices of lead exposure, which are based upon lead-induced upset of heme synthesis, are not considered acceptable. They include urinary delta-aminolevulinic acid (ALA), coproporphyrin excretion, and delta-aminolevulinic acid dehydratase (ALAD) in erythrocytes.

B. Confirming Studies

Lerner [2] has evaluated the analytical error in the dithizone colorimetric method for blood lead analysis performed at the Kettering Laboratory.

Thirty specimens, with an average size of 14 g, were taken in a single collection from one volunteer, then stored and frozen in vacutainers. Over the next ten months, blind samples were removed and sent for routine analysis. Blood lead values for the thirty specimens ranged from 12 to 28 μg lead/100 g blood. One sample which had a concentration of 42 μg/100 g was rejected from further statistical analysis, since it was an outlying value. The mean value and standard deviation of the thirty samples was 18.37 ± 3.90 μg/100 g. This exceeded the expected variability of ± 3.50 μg/100 g.

C. New Methods for Sampling

Since many of the new analytical methods for biological lead measurement use small volumes of blood (less than 50 μl), they offer an advantage toward sampling. Suitable samples are obtained by finger-stick. While this new method is faster and less painful than the macro-scale blood collection technique recommended by the NIOSH document [1], it is prone to contamination by inadvertant environmental lead sources and requires diligent attention [3,4]. Cooke et al. [3], for example, found that the soap which they were using for hand washing was contaminated by traces of lead. This contamination apparently affected their results which are discussed in the section on New Analytical Methods. Bratzel and Reed [4] suggest the following procedure for the finger-stick method: hands should be washed with a lead-free soap ("pHisohex" is acceptable), preferably with a scrub brush; rinse with deionized water; dry with gauze; spray with collodion and let dry; puncture the finger from the side with a lancet; wipe off the first drop of blood; and squeeze gently to bring up sample blood.

Some of the micro-scale analytical techniques discussed herein have used micro-scale blood specimens collected by two different methods: collection

in capillary tubes or as spots taken on filter paper. Marcus et al. [5] discussed some of the experimental problems of collecting blood in capillary tubes. The major difficulty concerns the inability of some commercially available tubes to adequately heparinize blood. While several commercially available heparinized capillary and caraway type tubes did not prevent some blood clotting, Marcus et al. [5] did judge one tube (distributed by Environment Sciences Associates of Burlington, Mass.) as suitable. The filter paper method consists of forming a blood spot (approximately 2-4 cm) by touching the paper to the finger blood drop, allowing it to dry and then punching small discs from the spot with a standard office paper punch. While the method is fast and simple, some experimental error can arise from variations in the lead distribution over the spot. Although lead content is apparently greater toward the periphery of the spot, the relative error can be neglected when discs of 4 to 6 mm are punched [6].

Rahn et al. [7] have developed an automatic filter changer for use in atmospheric lead sampling. The device is capable of changing 24 filters. Its design and use is applicable to the procedure designated by the NIOSH document [1].

Biles and Ellison [8] have evaluated three cellulose filter papers for atmospheric lead collection: Whatman No. 1, No. 4, and No. 541. Air was pumped through the filters at face velocities of approximately 6.5 cm/sec at the filter. They concluded that these filter papers were not suitable since more than half the atmospheric lead passed through.

D. New Analytical Methods

1. Atomic Absorption Spectroscopy

a. Biological Samples

Several procedures have been developed for lead analysis, especially for biological specimens, which use atomic absorption spectroscopy (AAS) to measure lead concentration. Kahn [9] and Sunderman [10] have reviewed basic principles of AAS and its application to lead analysis. The sample to be analyzed is nebulized by either a flame or other heat sources. This atomization reduces most of the lead to the atomic state, which can then absorb light from a hollow cathode lamp (usually using the lead wavelength at 283.3 nm). The measurement can use either the conventional flame system (usually air-acetylene) or one of several semi- or non-flame systems: Delves cup; graphite furnace; or carbon rod atomizer. The conventional flame system requires the aspiration of dissolved lead into the flame. For blood lead analysis the usual sample size is 5 to 10 ml of whole blood, which is comparable to the size needed for the recommended dithizone method [1]. The conventional system then requires a fairly long work-up to extract the lead from all organic matter and dissolve it into an aqueous medium. The semi- and non-flame procedures require micro samples (50 µl or less) and shorter work-up prior to AAS analysis. The disadvantages of the semi- and non-flame systems are that the small samples are more prone to contamination from extraneous sources and non-atomic absorbance interference during the measurement.

Murthy et al. [11] have developed a method for digesting and extracting lead from tissues and hair with tetramethylammonium hydroxide. The lead is subsequently measured by the conventional air aspiration method.

Kopito et al. [12] have evaluated sources of error and how to minimize them in four methods for blood lead work-up. The four procedures are those of Berman [13]; Blanksma [14]; Einarsson and Lindstedt [15]; and Kopito and Shwachman [16]. All require macro-scale blood samples and are used in

conventional flame AAS measurement. The methods of Berman [13] and Blanksma [14] are similar and consist of three stages: (1) precipitation of blood protein with trichloroacetic acid (TCA); (2) wash with water to remove the lead; and (3) lead removal from the wash by first chelating it with ammonium-1-pyrrolidine dithiocarbamate (APDC) and then extracting the complex into methyl isobutyl ketone (MIBK). The primary source of error is in the efficiency of removing lead from precipitated protein. With several washes, however, lead recovery is quantitative. The Einarsson and Lindstedt [15] procedure consists of precipitating whole blood with a mixture of TCA and perchloric acid. Lead is collected from the supernatant. When one precipitation is used, lead losses ranged from 23 to 30%; multiple precipitations reduce the percentage of lead lost. Kopito and Shwachman [16] wet ash the whole blood with a mixture of nitric and perchloric acids, and then coprecipitate the lead with bismuth chloride or nitrate. The critical step is the complete oxidation of all organic matter before the precipitation.

NIOSH has developed procedures for lead analysis in air [182], and blood and urine [183, 184]. Atmospheric lead determination requires the collection of particulates on a 0.8 μm (37 mm diameter) cellulose filter. The air is sampled (at 2 lpm and a minimum of 100 l) by a personal monitoring pump. The filter is wet ashed and the lead is dissolved with concentrated nitric acid. The sample is then diluted (with water) to a 10 ml volume and the lead is assayed by conventional flame AAS. The sensitivity is 2.3 μg lead (0.013 mg/cu m). In the range of 0.128 to 0.399 mg Pb/cu m the coefficient of variation was 0.072. Biological lead is digested with either concentrated nitric acid or a perchloric acid-nitric acid mixture. The lead is chelated and extracted into an organic solvent. P&CAM 101 [183] suggests chelation

with ammonium pyrrolidine dithiocarbamate and extraction with methyl isobutyl ketone. Nine analyses of an NBS lead standard (1.00 $\pm$ 0.023 µg/g) yielded a value of 0.99 $\pm$ 0.064 mg/g [185]. P&CAM 102 [184] describes a procedure in which the lead dithizonate complex is formed and extracted into chloroform. The accuracy is reported as 97 $\pm$ 2% and the coefficient of variation as 6%.

The Delves cup system is a semi-flame modification of AAS which has been developed to analyze micro samples of whole blood with less laboratory work-up than required for conventional flame AAS. It can also be applied to analysis of lead in urine or from the atmosphere. Two procedures have been developed for use with the system for blood lead analysis. The blood can be added either directly or impregnated on a small, filter paper disc.

In the original procedure, Delves [17] added 10 µl aliquots of whole blood to nickel foil crucibles. The organic matter was oxidized by heating the blood with 20 µl of a 100-volume H_2O_2 solution at 140°C on a hot plate. Complete digestion of all organic matter was essential. After the sample was heated to dryness, the crucible was placed into the Delves AAS system. Delves found a minimal detection limit of 1.19 µg lead/100 ml of whole blood (at 283.3 nm). Standard deviation was reported as ± 4% at 3 ng lead and sensitivity was 1 x 10^{-10} g for 1% absorption. Delves compared 39 duplicate whole blood analyses by this method to determinations by the standard dithizone method [1]. For samples ranging from 19 to 245 µg lead/100 ml blood, the correlation coefficient of the two methods was 0.989. The Delves system yielded lower values than the dithizone method. Delves stated that 48 determinations per day can be performed with 16 crucibles.

Marcus et al. [5] reported the experience of the New York City Department of Health Laboratories with the Delves system. Experimental problems

Table II-1. Results of Replicate Analyses of Four U.S. HEW Blood Standards (Same Technician) By the Delves Cup AAS Method[a]

	Sample "B"	Sample "D"	Sample "H"	Sample "K"
		µg/liter		
Mean	309	493	802	1258
SD	188	387	423	528
Variance	355	1498	1790	2792
SE	54	107	117	136
CV %	6.09	7.85	5.27	4.20
HEW Value[b]	300	480	870	1240

[a] Source: Marcus et al. [5]
[b] Flame AAS Method

include blood sampling, alignment of the Delves cup system within the AA flame (a trial and error effort), baseline variations, and the deterioration of the nickel crucibles with use. A comparison was made of the Delves cup method with conventional flame AAS in a double blind study. Comparative values for lead content were 273.2 ± 99.0 µg/ℓ (flame AAS) and 276.6 ± 105.8 µg/ℓ (Delves system); this showed no significant difference for the two methods ($p > 0.05$). Table II-1 summarizes their evaluation of four specimens from the B.C.E.M. Childhood Lead Poisoning Control Branch, U.S. H.E.W. The results had a reproducibility of ± 11.5% (95% confidence interval) and a coefficient of variation (CV) equal to 5.75% ± 1.9.

Hicks et al. [18] modified the original Delves procedure [17] by using 20 µl of 30% H_2O_2 in the digestion. They compared this modification with conventional (flame) AAS using the work-up procedure of Berman [13] (which is briefly described on page 7); the correlation coefficient of the results was 0.96. They also evaluated the accuracy by analyzing samples whose lead content was previously analyzed in a U.S.P.H.S. quality control survey (which included the recommended dithizone method); the correlation coefficient for these results was 0.98. Precision was evaluated with 50 replicate analyses, which yielded a value of 46 ± 3.7 µg/100 ml and a variability of 8%. When they compared lead concentrations determined for their modification using venous and capillary blood, they found a correlation coefficient of 0.93. They also reported that a deuterium arc background corrector eliminated errors from non-atomic absorption, which is caused by the light reflectance off of smoke produced when the sample is atomized.

Rose and Willden [19] modified the Delves procedure by substituting aqua regia for hydrogen peroxide (in the digestion) and replacing the

Table II-2. Comparison of Results Obtained by Using the Rose and Willden Modification and the Original Delves Procedure on Replicate Blood Samples[a]

Method	Number of assays	Mean/µg per 100 ml	Range/µg per 100 ml	Standard deviation
Delves' method (with the original matched cups)	15	69.26	59 to 79	4.32
Delves' method (with quartz cups)	15	67.13	47 to 79	8.96
Aqua regia method (with unmatched cups)	20	68.60	60 to 77.5	4.93
Aqua regia method (with matched cups)	20	68.25	64 to 72	2.49

[a]Source: Rose and Willden [19]

Table II-3. Comparison of Analyses for Lead in Urine by the Delves Cup System and by the Modified Method of Torres*[a]

Sample	Modified Method of Torres (mg/liter)	Untreated Urine by Delves Cup (mg/liter)	Amount Added (mg/liter)
1	0.027	0.028	0.030
2	0.032	0.041	0.042
3	0.050	0.053	0.050
4	0.057	0.068	0.064
5	0.072	0.076	0.076
6	0.087	0.086	0.092

*Values are averages of three to five results

[a]Source: Anderson and Mesman [20]

Table II-4. Comparison of Analyses for Lead in Urine by the Delves Cup System and by Dithizone Colorimetry*[a]

Sample	Dithizone (mg/liter)	Untreated Urine by Delves Cup (mg/liter)	Amount Added (mg/liter)
7	0.034	0.054	0.050
8	0.012	0.033	0.030
9	0.100	0.089	0.090
10	0.010	0.022	0.020
11	0.040	0.066	0.070
12	0.038	0.059	0.060

*Values are averages of three to five results

[a]Source: Anderson and Mesman [20]

nickel crucibles with quartz crucibles. This modification provides a better digestion of organic matter in the blood. Table II-2 compares values of replicate samples analyzed by the modified procedure using matched and unmatched quartz crucibles and by the original Delves procedure. Matched and unmatched refer to equal or unequal numbers of analyses in each cup.

Anderson and Mesman [20] used the Delves cup system for urine lead analysis. They used a deuterium arc background corrector to eliminate errors from non-atomic absorption. A simplified procedure was evaluated in which 20 µl of untreated urine in a nickel Delves cup was dried and smoked to remove organic matter before AAS measurement. An additional procedure was examined (method of Torres [21]) in which lead is extracted from the urine into methyl isobutyl ketone with dithizone and then returned to aqueous solution followed by analysis in the Delves cup system. A comparison was made of the basic procedure with the modified method of Torres (Table II-3) and with the colorimetric dithizone method (Table II-4). While the Delves procedure and the modified method compared well, the colorimetric method did not. Anderson and Mesman [20] acknowledged that they were not familiar with the colorimetric method and attributed the low values to their lack of experience. Among 60 samples analyzed by the basic Delves procedure, they found a minimal detection limit of 0.02 mg lead/l urine (or 0.4 µg lead) and an error of $\pm$5%.

The carbon furnace and carbon rod atomizer are non-flame AAS adaptations [9, 10]. Samples are introduced with or without laboratory pretreatment, dried, organic matter destroyed during an ashing stage, and lead is atomized. All operations require an inert gas atmosphere. Since smoke is generated during the atomization phase, a deuterium background corrector is necessary to compensate for non-atomic absorption.

Evenson and Pendergast [22] and Fernandez [23] have evaluated the use of the Perkin-Elmer Models HGA-2000 and HGA-2100 graphite furnaces for the analysis of whole blood specimens for lead. Results from both laboratories [22,23] were similar. Blood specimens were heparinized, diluted, introduced into the graphite furnace, dried (ca. 125°C), and ashed (ca. 525°C) prior to AAS measurement. Evenson and Pendergast reported that ash build-up accompanied by an increase in lead absorbance occurred, but stabilized with time. Using the older model HGA-2000 only, they found lead recovery from spiked, whole blood samples ranged from 62 to 87% (mean 75%). Fernandez [23] found a 98% recovery from whole blood, which contained lead at 150 to 1000 µg/l, using the HGA-2100. Fernandez also compared the use of both model furnaces to conventional AAS analysis in a double blind study. While he found a correlation coefficient of 0.98 for the HGA-2100, he found a consistently lower correlation (range from 0.79 to 0.88) for the HGA-2000. Table II-5 describes the reproducibility for day-to-day measurements and within-run variations using the HGA-2100. These investigators [22,23] also examined the effects of some anticoagulents, cations, anions, and acids on the lead AAS signal. The most noticeable effects were decreases in absorbance caused by high concentrations of potassium, sodium, or citrate or pH > 5.

Baily and Kilroe-Smith [24] have evaluated the following seven procedures for whole blood work-up in the graphite furnace measurement of blood lead:

(1) 0.5 ml of blood plus 4.5 ml of doubly distilled water

(2) 0.5 ml of blood plus 4.5 ml of 0.01 M HCl

Table II-5. Reproducibility of Blood Lead Measurements at Various Concentrations of Lead by the Method of Fernandez [23]

Sample No.	Mean	SD	CV, %
	µg/liter		
Within-run reproducibility[a]			
1	140	6	4.1
2	350	8	2.4
3	540	16	2.9
Day-to-day reproducibility[b]			
10	126	11	9.1
11	266	15	5.7
12	380	16	4.2
13	512	19	3.8
14	720	29	4.1

[a]Based on 10 repetitive determinations
[b]Based on five determinations over a five-day period

(3) 0.5 ml of blood plus 4.5 ml of 2% Triton X

(4) 0.5 ml blood plus 1.0 ml of Unisol. Let the mixture stand overnight, then add 3.5 ml of doubly distilled water

(5) Similar to (4) except the 3.5 ml of water was not added until the solution was clear

(6) A modified Einarsson and Lindstedt [15] procedure (see page 7) in which blood was digested with a perchloric and trichloroacetic acid mixture

(7) The method of Mahin and Lofberg [25] in which heparinized blood is treated with perchloric acid and H_2O_2

They found that lead losses occurred when ashing temperatures exceeded 500°C, but that high background non-atomic absorbances interferred if temperatures below 500°C were used with methods 1 through 5. They concluded that the Einarsson-Lindstedt modification (method 6) was the most convenient, reproducible, and reliable method of analysis.

Posma et al. [26], Ealy et al. [27], and Kubasik and Volosin [28] have examined carbon rod atomization (CRA) for blood lead analysis; Kubasik and Volosin [29] have also used it for urinary lead determination. These investigators used either the Varian CRA Model 61 or Model 63 and corrected for non-atomic absorbance with a deuterium arc background corrector. The general procedure for CRA corresponds to the steps used in graphite furnace techniques: the sample is transferred to the carbon rod, dried, ashed, and then atomized for AAS measurement.

Ealy et al. [27] diluted heparinized whole blood with doubly deionized water before injecting a 10 µl sample into the CRA. With this procedure, they observed a detection limit of 2 µg lead/100 g blood and a sensitivity of 5 µg lead/100 g blood (for 1% absorption). They compared this method to analysis by isotopic-dilution spark source mass spectrometry using 204 Pb, and found that the values agreed.

Kubasik and Volosin [28] compared direct CRA analysis of heparinized whole blood to analysis of a sample diluted 2:1 with Triton X-100. The dilution technique yielded better results. While the coefficient of variation of three pooled blood specimens (20 samples for each group) ranged from 6.1 to 10.7% for direct analysis, the dilution procedure results ranged from 2.1 to 4.8%. They also noted that ashing was a greater problem with the direct procedure.

Posma et al. [26] used nitric acid to aid the digestion of organic matter in blood. In their method, 10 µl of a 1% nitric acid solution and 5 to 10 µl of heparinized whole blood are placed into the CRA cup. The usual procedure of drying, ashing, and atomization was then followed. Since their modification released less smoke than direct CRA analysis, the background non-atomic absorbance was also reduced. They compared the method with conventional AAS analysis (chelation by ammonium-pyrrolidine dithiocarbamate and extraction into methyl isobutyl ketone) and obtained a correlation coefficient of 0.9974. Table II-6 provides the results for the two procedures.

Filter paper discs impregnated with blood have been used for lead analysis by the Delves cup system [3,30-32] and CRA [6]. The technique requires that a blood spot is formed on a piece of filter paper, allowed to dry in air, and discs are punched from the spot with a standard office paper punch. The advantages of the paper disc method include the elimination of the need for heparinizing or refrigerating blood collected in tubes. Cernick [6] noted sampling problems as the result of red cells distributing with a slight build-up along the periphery of the blood spot. He found that this difficulty will not affect results if blood drops of 0.02 to 0.04 ml are applied to the filter paper and discs are cut to 4.0 mm (diameter) or larger.

Table II-6. Comparison of Results for the Carbon Rod Atomization Procedure of Posma and Coworkers [26] with Conventional Atomic Absorption for Analysis of Heparinized Whole Blood

	Carbon Rod Method of Posma and Coworkers	Macro Analysis by Conventional Atomic Absorbance
Detection Limit (ppb)	15.0	40.0
95% Confidence Interval (ppb)	±38	±33
Sensitivity (1% Absorption Signal)	5.0	160.0
Analytical Rate[a]	40.0	20.0

[a]Number of analyses which can be performed per day

Cooke et al. [3], Fox and Sayers [30], Mehkeri et al. [31], and Bogden and Joselow [32] used the Delves cup system with punched paper discs. Their procedure was to ash the sample, then analyze. Because of sample smoking, deuterium arc background correctors were used. The four groups compared the punch disc approach with a variety of alternative analytical techniques (Table II-7). The best correlations (ca. 90%) were obtained when multiple samples were analyzed and averaged. Although Cooke et al. [3] found a correlation coefficient of the disc in a cup method with dithizone colorimetry of 0.78, they considered the method an adequate procedure for routine screening to evaluate whether an individual had exceeded the safe blood lead limit (ca. 400 µg/l). They found that the micro disc method tended to yield false positive rather than false negative results. It was suggested that the high false positives might have resulted in part from inadvertent sample contamination.

Cernick [6] noted that nickel Delves cups are rapidly deteriorated by the burning discs and evaluated CRA as an alternative procedure. He found that the carbon rod resisted deterioration. Absolute sensitivity of the method was 25×10^{-12} g. Standard deviation was calculated for three blood lead concentrations (11 replications for each concentration): at 16 (±1.65); at 67 (±3.87); and at 99 µg lead/100 ml blood (±3.85).

b. Atmospheric Samples

Kneip et al. [33] replaced the colorimetric dithizone method with conventional (flame) atomic absorption for the analysis of atmospheric lead. Atmospheric samples were collected by drawing the air through membrane or glass fiber filters. The filters were ashed and lead was extracted with a mixture of nitric and hydrochloric acids. The resulting aqueous lead

Table II-7. Comparison of the Blood Lead Analysis By Delves Cup System Using Punched Filter Paper Discs to Independent Measurements

Reference	Disc Size	Comparison Method	Correlation Coef.	No. of Discs Analyzed
Fox and Sayers [30]	6.5 mm	Cathode ray Polarography	0.89	2
Bogden and Joselow [32]	1/4 in.	Conventional atomic absorption	0.9	3
Cooke et al. [3]	5 mm	Dithizone colorimetry	0.78	1
Mehkeri et al. [31]	7 mm	Conventional Delves cup system	0.89	3

solution was then analyzed by air aspiration into an air-acetylene flame. The 217 nm wavelength was used rather than the more often employed 283.3 nm wavelength. Standard deviation was estimated at ±10% (and recovery at 82%). This method requires a 200 liter sample for an atmospheric concentration of 0.01 mg lead/cu m air.

Woodriff and Lech [34] have developed a method for AAS analysis of atmospheric lead which does not require any laboratory work-up. The atmospheric samples must be pumped through crucibles made of spectral grade graphite and with dimensions of 16 mm long by 6 mm O.D., and 4.77 mm I.D., and drilled to 7 mm. Sample volumes were 100 to 500 cc of air. After sampling, the crucible is placed into a graphite furnace and the AAS measured. Sensitivity was 5×10^{-12} g (for 1% scale deflection) and the reported coefficient of variation was ±1.2%.

Matousek and Brodie [35] used a slightly modified approach for analysis of atmospheric lead. They pumped samples (volumes of 200 cc) through graphite sampling cups fitted with Millipore filters. Excess phosphoric acid was added to the cup; it was inserted into a CRA (Varian Model 63), and the sample was treated by the usual drying, ashing, and atomization sequence. Absolute sensitivity (for 1% absorption) was 1.7×10^{-11} g (or 0.1 µg lead/ cu m for a 200 ml sample). Relative standard deviation (for approximately 1 µg lead/ cu m) was ±4.2%.

Noller and Bloom [36] used the Matousek and Brodie [35] procedure in field studies. They found a sensitivity (for 1% absorption) of 1.7 µg/cu m lead and a detection limit of 0.48 µg/cu m for a 200 cc volume sample. The relative standard deviation ranged from 7.8 to 51.1% for samples containing 0.3 to 8.6 µg lead/cu m air.

2. Methods of Lead Analyses Other than Atomic Absorption Spectroscopy

Seeley and Skogerboe [37] used graphite cups similar to the design of those reported by Woodriff and Lech [34] for atmospheric lead sampling and subsequent analysis by emission spectroscopy. They added indium as an internal standard to each graphite filter prior to sampling. Samples were analyzed with the carbon rod atomizer at the 283.3 nm lead line. Absolute detection limit for lead (added directly to the filters) was 3 ng. They estimated precision for the emission method at $\pm$10 to 20% whereas standard AAS had a precision of $\pm$5% or better. Human and Norval [38] employed atomic fluorescence spectroscopy for lead analysis on whole blood specimens. The only pretreatment consisted of diluting the blood with doubly deionized water. Analysis was made with an argon-hydrogen-oxygen flame using the 405.8 nm lead wavelength, which yielded a better signal to noise ratio than the 283.3 nm wavelength. The detection limit for this method was 0.0012 µg lead/ml blood and precision was better than 4% at 200 µg lead/ml blood. Sodium was the only reported interference.

Direct current arc emission spectrography has been used for lead analysis in tissues [39] and in atmospheric samples [40]. The method is able to simultaneously analyze for several metals rather than for lead alone. The technique consists of adding a known amount of a metal (germanium or indium) not present in the sample as an internal standard, obtaining the emission spectrum, and then measuring lead concentration by comparison of the relative intensities of lead lines (to the internal standard) with standard

curves. Yoakum et al. [39], who measured lead concentration in biological tissues, wet ashed the samples with sulfuric acid. They reported a detection limit for lead at approximately 0.01 to 0.02 µg lead/electrode and a precision of ±15% or better. Sugimae [40] determined atmospheric lead, which was collected on membrane filters (Gelman DM-800). Preliminary work-up consisted of dissolving the membrane in acetone and collecting residues, which included the lead, by centrifuge. Standard deviation (8 determinations) was 6.1% for samples containing 2200 µg lead/g residue.

Searle et al. [41] and Duic et al. [42] have evaluated anodic stripping voltametry (ASV) for blood and urinary analyses. Sampling and pre-treatment used by both groups of investigators were similar. Blood samples of 50 µl or urine samples of 500 µl were digested with perchloric acid or a mixture of perchloric-sulfuric acid; the mixed acid apparently digested blood samples faster than perchloric acid alone. The digested samples were then diluted with distilled water and lead was measured. Duic et al. [42] reported a ±5% deviation for blood lead measurements. Both Searle et al. [41] and Duic et al. [42] compared ASV to conventional AAS lead determination. Duic et al. [42] found that AAS yielded consistently lower lead concentrations. Searle et al. [41] obtained a correlation coefficient of 0.87 between ASV and AAS for 200 blood samples. Table II-8 compares replicate analyses of blood lead by conventional AAS and ASV. Searle et al. noted that equipment costs are less for ASV than for AAS and that both methods require equivalent technician skills. They suggest that ASV method would be suitable in laboratories where less than 25 samples per day were analyzed.

Several relatively simple methods for rapid and efficient lead analyses have been developed which use colorimetry or simple fluorescence

Table II-8. Comparison of Results for Blood Lead, As Determined By Atomic Absorption and By Anodic Stripping[a]

No. Samples	Total Pb Present	Pb Recovered, av	SD	CV, %	Volume of Blood, ml
		µg/100 ml			
Atomic absorption					
12	23	17	0.91	5.4	3.5
12	33	35	2.09	6.0	3.5
12	53	53	0.91	1.7	3.5
12	83	85	2.24	2.6	3.5
Anodic stripping					
12	23	29	2.26	7.8	0.10
12	23	30	4.22	14.1	0.05
12	33	34	1.13	3.3	0.10
12	33	32	2.40	7.5	0.05
12	53	57	2.27	4.0	0.10
12	53	58	3.16	5.4	0.05
12	83	85	4.10	4.8	0.10
12	83	83	2.49	3.0	0.05

[a]Source: Searle *et al.* [41]

measurements. Reisfeld et al. [43], Skuric et al. [44], and Ronneau et al. [45] have developed methods for atmospheric lead analysis in which particulates are collected and analyzed on filter paper. Ryan et al. [46] has developed a rapid method for blood lead analysis.

Reisfeld et al. [43] used the complex between lead (II) and carminic acid under alkaline conditions to form a blue colored derivative. Lead concentration was measured by reflectance spectroscopy at 600 nm. The lower detection limit was 5 ppm. While copper (II) and iron (II) were interferences, twelve other cations were not, including Ba (Ba), Ca (II), Mg (II), Na (I), K (I), Cd(II), Fe (III), and Ni (II).

Skuric et al. [44] used a ring oven method for analysis of lead in atmospheric samples collected on filter paper. The filter paper sample was treated with sulfuric acid and soluble sulfates were washed off. The tetrachloroplumbate ion, $(PbCl_4)^{-2}$, was subsequently formed by treatment with 0.1 M sodium chloride. Lead concentration was measured by comparing the fluorescence of the sample rings under a mercury vapor lamp with that of standard rings. They reported a sensitivity of 0.5 μg lead and a standard deviation of 20 to 30% for the range 0.1 to 5 μg lead. They evaluated the potential interferences of 29 anions and cations and reported interferences by permanganate, barium, and bismuth.

Ronneau et al. [45] developed a variation of the ring oven method in which lead is eluted off the collection filter paper with 0.1 M nitric acid onto a cellulose strip and concentrated into a 0.5 to 1 mm zone. The strip was then sprayed with sodium rhodizonate, which forms a red complex with lead. Estimation by visual comparison to standards was possible down to a minimal detection limit of 10 ng.

Ryan et al. [46] have developed a fluorescence method for blood lead determination. Their procedure required mixing and heating the sample with nitric acid, calcium chloride, and ammonium oxalate. Lead and calcium were coprecipitated by titration with ammonium hydroxide and the CaO:Pb phosphor was subsequently produced by igniting the precipitate at 850 to 900°C. Lead was measured by its luminescence at 530 nm. The analytical working range was 5 to 2000 ng/ml. Co (II), Mn (II), and Ni (II) were reported to interfere with this method.

Activation analysis and X-ray fluorescence have been evaluated for measurement of lead on filters from atmospheric sampling [47-49]. The advantages of the methods include that the filters used for atmospheric sampling do not require any laboratory treatment, that filters can be re-analyzed, and that several metals can simultaneously be analyzed. Disadvantages include equipment costs and analytical time per sample. Hammerle et al. [47] compared X-ray fluorescence measurement to AAS for analysis of lead on three filters used for collecting atmospheric samples. The two methods yielded values of lead concentrations which were within experimental error. Aras et al. [48] measured lead concentrations by photon activation analysis; accuracy for the method was estimated at ±5%. The required analytical time (about one week) and equipment limit the use of this method for any monitoring. Parsa and Markowitz [49] developed a ^{3}He activation analysis procedure for lead. The ^{3}He reacts with lead to yield the radioactive ^{207}Pb. The lead content on a sampling filter can be calculated by the increase in radioactivity. The detection limit was about 50 pg/cm^2 of collecting filter surface area. Absolute accuracy was estimated at 9 to 12% and agreed with X-ray fluorescence measurement within 3 to 5%.

3. Biological Indices of Body Lead Burden

Several biological parameters provide indices of body lead burden [1,50]. Most indices reviewed herein measure lead interference with erythrocyte porphyrin metabolism [51-58]; one paper evaluated radiological analysis of skeletal lead deposits [63].

Lead interferes with the metabolic processes of the enzyme δ-aminolevulinic acid dehydrogenase (ALAD). ALAD catalyzes the dimerization of two moles of δ-aminolevulinic acid to yield one mole of porphobilinogen [51]57). Lead concentration is inversely related to the activity of erythrocyte ALAD activity and directly to urine δ-aminolevulinic acid (ALA) concentration, and can be assessed by either measurement. Both approaches ultimately depend upon the method of ALA measurement. Basically all ALA measurements consist of the following approach: ALA is first condensed with either ethyl acetoacetate or acetylacetone to produce ALA-pyrrole, which is then reacted with a modified Ehrlich's reagent (para-dimethylaminobenzaldehyde in glacial acetic acid plus perchloric acid). ALA concentration is subsequently measured by the absorbance of the pink derivative at 553 nm.

While 23 to 440 μg ALA/100 ml urine is considered a normal adult range, adults with heavy occupational exposure to lead range from 380 to 28,500 μg ALA/100 ml urine. Roels *et al*. [52] has compared four methods for urine ALA measurement: Mauzerall and Granick [59]; Davis and Andelman [60]; Grabecke *et al*. [61]; and Lauwerys *et al*. [62]. The former two methods are similar procedures in which ALA is first separated from the interference porphobilinogen by ion exchange chromatography. Both methods yield consistently identical results. Lauwerys *et al*. [62] developed an automated procedure in

which ALA is added as an internal standard. While its results are slightly lower than the former two methods at ALA concentrations less than 6 mg/ml (urine), they were almost identical above that concentration. The Grabecki et al. [61] method yielded results consistently lower by about one-third. Tomokuni and Ogata [53] and Tomokuni [54.55] found that extracting the ALA-pyrrole with ethyl acetate is a simplified replacement for the ion exchange chromatography method to remove porphobilogen.

ALAD activity as a body lead burden index measures the rate of porphobilinogen production (ALA loss) per ml of blood erythrocytes in one hour at 38°C [50,51,54-57]. Kneip et al. [56] evaluated sources of error in ALAD determination and concluded that the major source of error is lead loss to walls of vacutainers, which are used for blood sampling. The Vacutainers are treated with acid to remove any traces of lead. Vacutainer walls retain anions which can compete with ALAD for lead. Lead loss to the wall results in enzyme reactivation.

Lamola et al. [57] used zinc protoporphyrin (ZPP) concentration as an index of blood lead concentration. Analysis of ZPP consists of diluting whole blood (1:500), adding dimethyldodecylaminoxide and measuring the fluorescence at 594 nm (excitation at 424 nm). Lamola et al. found a correlation coefficient of 0.87 for ZPP and blood lead concentration (by AAS). Iron deficiency anemia will also reduce ZPP concentration.

Soulsby and Smith [58] have developed a simplified method for estimating urinary coproporphyrin as a lead exposure index [50]. Urine samples are acidified with acetic acid and coproporphyrin is extracted into ether. The ether extract is shaken with an iodine-hydrochloric acid solution

which oxidizes any coproporphyrinogen to coproporphyrin. Concentration is measured by absorbance at the Soret band peak (ca. 401 nm).

Smulewicz [63] has discussed the use of lead lines at the iliac crest to diagnose the early stages of lead poisoning in children. The method was not discussed for adults, and does not appear to be a viable method for occupational monitoring.

III. HUMAN EFFECTS

A. Biological Monitoring - Measures of Lead Exposure and Biochemical Indicators of Response

Exposure to inorganic lead is manifested by alterations in a number of biologic parameters which can be readily assayed and quantified. In addition to the direct measurement of lead in whole blood or urine, other available techniques are based on the well-known inhibitory effect of lead on heme synthesis, with its associated enzyme inhibitions and product accumulations. Thus it is possible to monitor for responses to lead exposure by measuring urinary coproporphyrin, urinary delta-aminolevulinic acid (ALA), erythrocyte delta-aminolevulinic acid dehydrase (ALAD), and erythrocyte protoporphyrins.

The presence of lead in the blood and urine is clearly the result of exposure, but indicates nothing about a biological response. The present criteria document regarding inorganic lead considers the most practical test for monitoring lead absorption to be the determination of lead in whole blood (expressed as µg/100 g or µg/100 ml). This conclusion is supported by the Lead Industries Association [64]. However, several investigators have recently suggested that blood lead is an inadequate measure of occupational exposure. Vitale and coworkers [65] reported that abnormal renal function attributable to lead nephropathy had occurred among workers whose blood lead levels were below the recommended maximum concentration (80 µg/100 g). Similarly, McRoberts [66] examined several cases of lead poisoning in which whole blood lead levels were unreliable indicators of overexposure; however, a positive shift in the circulating plasma/erythrocyte lead concentration ratio was associated with symptoms of intoxication. On the other hand, asymptomatic individuals showed a constant plasma/erythrocyte lead concentration ratio. Additional evidence has

been provided to further support the contention that whole blood lead levels are merely a reflection of transport to body tissues [88], and do not provide a meaningful indication of total body burden [87]. Therefore, it is suggested [89, 111] that whole blood lead is a reliable indicator only for very recent exposure. Moreover, wide fluctuations in blood lead levels are known to occur as a result of mobilization of stored lead [68, 71, 72], variability in analytical methods of analysis [69] and other dietary and physiological factors [67, 71, 84-86]. The significance of individual blood lead values must also take into account the number of circulating erythrocytes present at the time of measurement in order to adequately protect those who might be anemic [64, 69, 90].

The determination of lead in urine is generally considered to be a less reliable monitoring technique than analysis of whole blood. Nelson [73] has noted a poor correlation between blood lead and urine lead values among certain individuals, due to variability in urinary excretion capability. Stokinger [74] pointed out that urinary lead determination is more accurate than blood lead only for exposure to alkyl leads; probably because organic lead has a much shorter residence time in the blood. Vitale and coworkers [65] found urinary lead to be an insensitive measure of absorption, while Tola et al. [75] found urinary lead determination to be useful at the beginning of exposure but still less reliable than blood lead measurements. Recently, Kawai [76] studied the value of measuring urinary non-precipitable lead as an index of exposure as well as intoxication. The underlying theory was that in normal subjects urinary lead is excreted entirely as precipitable lead, but in workers chronically exposed or intoxicated by lead, a major fraction was found as non-precipitable

lead. Kawai found that the urinary non-precipitable lead fraction did not correlate with symptoms of intoxication or duration of exposure, but related only to the magnitude of current or recent lead absorption.

Numerous investigators have concluded that measurement of ALAD activity is one of the most sensitive biologic indexes of lead exposure currently available [65, 74, 75, 77-81]. Indeed, changes in ALAD have been called too sensitive an indicator, since its activity is partly inhibited at lead concentrations much lower than required for the production of adverse clinical symptoms [78]. Furthermore, ALAD serves no biological function in the mature red blood cell [82]. On the other hand, Secchi and coworkers [83] were able to show a direct correlation between erythrocyte ALAD activity and liver tissue ALAD activity; an organ in which ALAD has a significant function. The relatively slow regeneration of ALAD activity following cessation of lead exposure may also be a useful indication of lead absorption in the recent past [80, 96]. It is suggested that in screening programs for the prevention of lead intoxication, erythrocyte ALAD should be considered as a sensitive and reliable method of early detection from the lowest exposure levels up to those doses which produce clinical symptoms of poisoning [75, 78]. However, at least one recent study [91] has suggested that at subclinical concentrations of lead in whole blood (mean, 22.8 µg/100 ml), ALAD activity did not significantly correlate. It is apparent that the accuracy of ALAD assays can be influenced by blood storage time and temperature [92]; and the effect of lead on ALAD can be partly reversed by lowering of the incubation pH or heating at 60°C for five minutes [93]. Comparative studies [94, 95] have established that erythrocyte ALAD activity is specifically altered by lead exposure, and not by other heavy metals such as cadmium or mercury.

The determination of ALA in urine is regarded as a useful technique for biological monitoring in cases where lead exposure has exceeded the threshold level [74]. Several investigators have noted that increased urinary ALA excretion does not occur until erythrocyte ALAD activity has been markedly reduced [75, 77-79]. Thus, ALA in urine can be a more specific indicator of potentially toxic lead exposures than erythrocyte ALAD, which is severely depressed after absorption of lead in subclinical amounts. Tola [78] and others [77] have observed a rise in urine ALA only when blood lead levels reach approximately 40-50 μg/100 ml. The sensitivity of the urine ALA assay as a measure of lead-induced alteration in heme synthesis can be improved by correction for urine osmolality [97].

Recent advancements have been made in the development of accurate and sensitive indicators of lead exposure and its biological consequences. Clark [98] used fluorescence microscopy for excess erythrocyte porphyrin as a sensitive confirmatory method for the detection of chronic lead intoxication. Fluorescent erythrocytes appeared at blood lead concentrations of 50 μg/100 ml and preceded any significant decrease in hemoglobin values. The procedure is rapid, requires little blood, and may be performed on stored samples. Chisolm and coworkers [87] have reported that serial measurement of erythrocyte protoporphyrin by a simple fluorometric assay technique is a better predictor of the internal (chelatable) dose of lead than whole blood lead determination. This screening procedure is said to be highly useful for long-term monitoring of subclinical exposures and responses to therapy. Tomokuni and Ogata [106] have confirmed that the sensitivity of the fluorometric assay for erythrocyte protoporphyrin was almost equal to that of the erythrocyte ALAD test. Increases in erythrocyte protoporphyrin

appeared before elevated urinary excretion of ALA was evident. Most recently, measurement of zinc protoporphyrin blood levels has been employed as a sensitive and reliable index of biological response to lead absorption [111,179,180]. Therefore, as a measure of the toxic effects of lead on heme synthesis, many have found that erythrocyte protoporphyrin levels have good predictive value both as an initial screening test and in long-term follow-up [89, 107-110]. Moreover, in cases where blood lead levels and erythrocyte protoporphyrin levels disagree, it is probable that the latter index is more reliable and provides a better estimate of soft tissue lead [119].

Determination of the lead content of hair has been suggested as a possible screening procedure for measurement of the severity of exposure [99]. However, this technique has apparent limitations with regard to the age and sex of those exposed [100].

B. Relationship of Inorganic Lead Exposure to Biological Effects

Investigators in the past have favored the opinion that clinical signs of poisoning do not occur at concentrations of lead in whole blood less than 80 µg/100 g in adults or less than 40 µg/100 g in children [64, 70, 74, 82, 101]. This biological limit, however, is not particularly valid for all cases of lead intoxication, especially in adults [111,125,180]. Subclinical neuropathy has recently been reported in a group of 26 workers whose blood lead values had never exceeded 70 µg/100 ml [102]. On the other hand, a case has been presented [103] where levels of blood lead as high as 1,050 µg/100 ml were associated with only minor clinical symptoms. Differentiation between lead exposure and lead poisoning is obviously a difficult task based on blood lead values alone.

The concept of a blood lead threshold, however, has been addressed as a valid parameter for the setting of environmental standards [64]. Based on a statistical treatment of reference blood lead values obtained from a normal population, individual laboratories may adopt their own standards for excessive exposure. That is, for adults, blood lead values equivalent to the normal population mean +3 SD (standard deviations) would be the maximum allowable level. In children, the mean +2 SD would provide a reasonable measure of safety. Recognizing that interlaboratory variations in blood lead analysis are practically unavoidable, absolute reference values for normal blood lead cannot be formulated. Nevertheless, a reasonable degree of consistency should be evident in view of the belief that a worldwide mean for blood lead in adults is about 15-20 μg/100 g [82, 104]. Using the most recent data of McLaughlin and coworkers [105] as an example, mean blood lead values in 1971 from 798 non-exposed duPont workers throughout the U.S. was 19.5 μg/100 g (SD = 8.0). Thus, by the +3 SD guideline, a clearly "abnormal" blood lead value might be regarded as any level in excess of 43.5 μg/100 g. This figure does not imply, however, that signs of lead poisoning will be evident at this concentration; but it should alert medical officials to the need for reduction of exposure.

Correlation of subjective symptoms of intoxication with specific lead exposures in humans is difficult to generalize. Variability in results is commonly encountered due to differences in absorption, excretion, age, sex, and physiologic state [72, 102]. Adult male volunteers exposed to lead aerosols 23 hours per day for about 18 weeks at levels of 10.9 or 3.2 $\mu g/m^3$ achieved blood lead concentrations of 37 μg/100 ml and 27 μg/100 ml, respectively [72]. Blood lead reached a plateau concentration after about three months of exposure,

and returned to normal values two months after cessation of exposure. Urinary excretion of lead and depression of erythrocyte ALAD activity was evident only in the group treated at the higher dose; neither treatment, however, altered the excretion of heme precursors or produced symptoms of lead intoxication. Consistent with these results are the observations by Sakurai and coworkers [113] of 228 male workers exposed to varying amounts of lead. They showed that no dose-related increase in the subjective symptom rate occurred when blood lead values were 50 μg/100 g or less. Moreover, this level was shown to be an apparent threshold for obvious increases in urinary ALA excretion, and thus for biological response manifested as an alteration in heme synthesis. Three cases of mild lead poisoning were reported [114] in which blood levels of lead ranged from 109 to 139 μg/100 ml. Measurement of free erythrocyte protoporphyrin and urinary ALA confirmed the existence of a biological response; whereas urine lead level and urinary coproporphyrin excretion were unreliable indicators of exposure.

A synthesis of the results reported by numerous investigators provides a rough framework for the analysis of lead absorption and its subsequent biologic effects (Table III-1). Although it has been shown that each 1 μg lead/m^3 of air contributes about 1-2 μg lead/100 g of blood [82, 112, 113, 115, 116], extrapolation of this guideline to workroom situations may not be accurate without giving due consideration to particle sizes and solubilities, and variability from differences between samplers, days, and time-weighted versus actual values. Furthermore, the contribution to total body lead burdens from dietary sources and ambient air pollution is difficult to integrate into assessments of occupational exposure. Thus, current emphasis in the prevention of lead poisoning is being placed on prudent biological monitoring [64, 70] coupled with the control of lead emissions.

Table III-1. Correlation of Inorganic Lead Exposure to Biological Effects in Adults

Exposure Category	Blood Lead (µg/100 ml or g Whole Blood)	Biological Effects	References
Normal	15 - 20		82, 104
Subclinical Absorption	20 - 40	a. Erythrocyte ALAD	74, 75, 77-81, 94, 96 112, 113
Excessive Absorption Likely	40 - 60	a. Urinary ALA	74, 77-79, 113
		b. Urinary Coproporphyrin	75
		c. Erythrocyte Protoporphyrin	87, 89, 98, 107-110 119, 121
		d. Zinc Protoporphyrin Blood Levels	111, 179
		e. Hemoglobin Decreases	75
		f. Altered Spermatogenesis	135
Unacceptable Absorption	> 60	a. Central Nervous System Effects	111
		b. Peripheral Neuropathy	111
		c. Renal Damage	125, 180
		d. Gastrointestinal Disturbances	111
		e. Anemia	111, 180
Determination of Body Burden of Lead		a. Erythrocyte Protoporphyrin	119

C. Epidemiologic Investigations

It is often hoped that a systematic investigation of worker populations will supply the basis for a truly definitive association between the degree of occupational exposure to a harmful agent and its subsequent effect on health. In the case of inorganic lead, however, the data do not provide a completely satisfying explanation of dose-response relationships.

A retrospective examination of mortality data on 7,032 men employed in lead production facilities and battery plants from 1947 to 1970 was undertaken by Cooper and Gaffey [117]. Although problems were encountered in accurately interpreting death certificates, it was established that an excess number of deaths was attributable to "chronic nephritis or other renal sclerosis" and "other hypertensive disease." It was not possible to show an occupation-related effect on death due to stroke or hypertensive heart disease; however, suggestive evidence of increased deaths due to respiratory and gastrointestinal cancer was obtained. Life expectancy of lead workers did not differ significantly from U.S. males in general. Data taken from five U.S. lead plants in 1975 and 1976 showed evidence of hematologic, neurologic, and renal damage among numerous workers [180]. In every plant studied, unequivocal symptoms of lead poisoning were encountered; even among persons having blood lead levels of 81 μg/100 ml and with only two months of exposure.

A very recent report on the mortality of workers exposed to lead chromate [118] indicated that an excess of deaths due to respiratory cancer had occurred, and a high incidence of stomach cancer may also have been occupationally related. The small number of deaths involved, however, made statistical analysis of the data unjustifiable. In all of the plants studied, estimated time-weighted averages for both lead and chromium (VI) in air exceeded current and proposed standards.

Studies on symptoms of morbidity are somewhat more revealing than mortality studies in characterizing the adverse health effects of lead absorption at various levels. For example, Taylor and coworkers [120] have tabulated the incidence of lead poisoning symptoms among 35 men engaged in oxy-gas burning of lead-painted metal. Interpretation of their results (Table III-2) must take into account both that the mean hemoglobin value in exposed workers was 14.8 g/100 ml and that breathing zone lead concentrations in air ranged from 4,000 to 14,000 $\mu g/m^3$. The mean duration of employment in the worker group was 8.8 years (mean age 41 years). Biological testing to determine body burdens of lead (e.g., erythrocyte protoporphyrin or chelatable lead) was not performed.

A comprehensive study has recently been completed on lead disease among 158 secondary lead smelter workers [111]. Numerous biologic parameters were measured, including blood counts, blood chemistry, zinc protoporphyrin, nerve conduction velocity, reaction time, and the presence of classical clinical symptoms. A striking prevalence of central nervous system symptoms (fatigue, nervousness, anxiety, slowed mental function) was encountered even among workers with less than one year of exposure and blood values below 60 µg/100 ml (Table III-3). The incidence of central nervous system complaints was directly proportional to blood levels of zinc protoporphyrin but not blood lead (Table III-4). Other symptoms, including lead colic, reduced nerve conduction velocity, and reduced hemoglobin levels, were also associated with relatively short periods of lead exposure (typically less than one year). Symptoms of lead toxicity associated with long-term exposures were peripheral neuropathy and biochemical evidence of kidney function impairment. An important principle emerging from this investigation is the apparent unreliability of blood lead

Table III-2. Lead Levels of Blood and Urine, and Clinical Symptoms [120]

Population	Blood Lead (µg/100 ml)	Urine Lead (µg/l)	Colic	Constipation	Pallor	Lassitude	Blue Line
Group 1*	Mean = 91.0 (35 men)	Median = 144 (32 men)	4	3	4	4	5
Group 2†	Mean = 49.7 (34 men)	Median = 24 (32 men)	-	-	-	-	-

* Oxy-gas Burners.
† Controls.

Table III-3. Central Nervous System Symptoms and Blood Lead Levels [111]

Blood Lead Level (µg/100 ml)	Total Number Examined	CNS Symptoms Present		CNS Symptoms Absent	
		Number	%	Number	%
< 60	33	20	61%	13	39%
60 - 80	73	50	68%	23	32%
< 80	43	31	72%	12	28%

Table III-4. Central Nervous System Symptoms and Zinc Protoporphyrin Levels [111]

ZPP µg/100 ml	Total Number Examined	CNS Symptoms	
		Number	%
Less than 100	15	6	40%
100 - 200	28	15	53%
201 - 500	83	66	80%
More than 500	18	11	61%

levels in defining excessive absorption, and the good correlation of zinc protoporphyrin levels with anorexia, weight loss, lead colic, central nervous system symptoms, peripheral neuropathy, hemoglobin levels, and duration of exposure (Table III-5). Unfortunately, data were not available regarding levels of airborne lead in the plants studied. The distribution of blood lead levels among the workers and controls is shown in Table III-6. Although many of these workers had undergone chelation therapy, the mean level of blood lead in these men was actually higher than the mean level in those without a past history of chelation therapy. In addition, elevated levels of zinc protoporphyrin and a higher prevalence of clinical symptoms were found among those having undergone chelation therapy. The high incidence of lead intoxication in the absence of elevated blood lead values in this study indicates that biological monitoring for responses to lead (as opposed to air and/or blood lead sampling) may be necessary for adequate worker protection.

When Shannon and coworkers [122] examined rates of sickness absence among a group of 955 male lead workers they found no increases which were attributable to the lead exposure. The mean blood lead concentration for all workers was 55.4 μg/100 ml.

Very recently, a new dimension was added to the occupational hazards of lead exposure when reports were made of increased lead absorption in the children of lead workers [153, 154]. Contamination of household dust by lead brought home on the worker's clothing was believed responsible for the observed effects in children. These effects included elevated blood lead values and erythrocyte protoporphyrin levels. In some of the lead intoxicated children, hospitalization and chelation therapy were required.

Table III-5. Mean Blood Lead Levels and Mean Zinc Protoporphyrin Levels in Secondary Lead Smelter Workers, According to Duration of Exposure, and in a Control Group Without Significant Lead Exposure [111]

Duration of Lead Exposure (Years)	Number Tested	Blood Lead Levels (µg/100 ml) Mean ± SD	Number Tested	Zinc Protoporphyrin Levels (µg/100 ml) Mean ± SD
< 0.1	3	69.4 ± 6.6	2	66 ± 35
0.1 - 0.29	12	64.51 ± 11.4	11	160 ± 126
0.3 - 0.9	31	65.4 ± 15.0	30	244 ± 140
1.0 - 2.0	60	73.8 ± 15.8	58	343 ± 166
3.0 - 9.0	30	72.6 ± 19.3	29	303 ± 154
> 10	15	78.1 ± 17.1	15	369 ± 136
Controls	23	38.0 ± 9.4	21	48 ± 21

Table III-6. Blood Lead Levels (µg/100 ml) in Secondary Lead Smelter Workers, and in Workers with No Significant Lead Exposure [111]

Blood Lead Levels	Number of Lead-Exposed Workers	%	Number of Non Lead-Exposed Workers	%
Less than 40	2	1%	14	58%
40 - 59	34	22%	10	42%
60 - 79	75	48%	0	0%
More than 80	45	29%	0	0%
Total	156		24	

D. Lead Toxicity in Humans

1. Neurotoxicity

In 1972, Whitfield and coworkers [123] reviewed 54 cases of lead encephalopathy in adults; 31 identified from the scientific literature, and 23 from the records of the University of Alabama Medical Center. Lead exposure usually occurred by ingestion of moonshine liquor, and symptoms ranged from confusion and disorientation to seizures, coma, and death. The authors pointed out that while the differential diagnosis of lead encephalopathy is extremely difficult, this condition is the most life-threatening consequence of lead exposure. It was further noted that lead encephalopathy rarely occurs from industrial exposure. However, Segal et al. [124] described three cases in 1974 of lead encephalopathy from industrial poisoning. All three patients (2 men and 1 woman) had elevated blood levels (90, 316, and 180 μg/100 ml) and presented a diversity of neurological signs.

Seppäläinen and coworkers [102] recently presented important evidence documenting the existence of subclinical neuropathy associated with low levels of lead in the blood. Measurements of motor nerve-conduction velocity in 18 men and eight women with occupation-associated blood lead values ranging from 20 to 70 μg/100 ml showed reduced function in comparison to sex-matched controls ($p < .001$). These results were in agreement with previous findings by the same investigators. The authors felt that the demonstration of subclinical neuropathy attributable to lead absorption should be considered more serious than alterations in heme synthesis, due to the poor regenerative capacity of the nervous system.

Petkau and associates [129] have described a case of amyotropic lateral sclerosis (ALS) possibly related to a six month exposure to high levels

of white lead. Early clinical symptoms in this patient were more consistent with lead-induced polyneuropathy than ALS, and elevated urinary excretion of lead confirmed excessive exposure. At necropsy, increased levels of lead were found in the spinal cord, nerve, and muscle. Other cases of ALS examined by the authors in which exposure to lead was not suspected similarly revealed elevated levels of lead in the tissues. In 1976, Conradi and coworkers [181] confirmed the association of excessive lead absorption with ALS. These investigators observed that the lead content of cerebrospinal fluid was elevated in 12 patients with ALS when compared to controls having non-degenerative neurological conditions. A hypothesis was offered concerning the pathogenesis of lead in ALS based on the abnormal availability of lead to the nervous system in the disease. Westerman and coworkers [130] were not able to correlate lead absorption with the development of multiple sclerosis in humans.

2. Renal Damage

Occupational lead nephropathy in adults is a relatively uncommon occurrence in the United States and, thus far, has been poorly characterized in its pathogenesis. However, recent studies have suggested that chronic lead nephropathy may be going unrecognized due to a lack of correlation with blood lead concentrations. An excessive incidence of kidney dysfunction (elevated blood urea nitrogen and creatinine) was found among lead plant workers [111, 180]. The prevalence of abnormal findings was strongly correlated with duration of exposure to lead, even though blood lead levels did not correlate with length of exposure. Wedeen and associates [125] examined 13 lead workers suspected of having excessive body burdens of lead. Two of the patients had been hospitalized for lead colic, but none of the group displayed clinical symptoms of renal dysfunction. Laboratory tests revealed that one patient was suffering

from asymptomatic renal failure, while five others showed signs of preclinical renal dysfunction. Based on blood lead values alone, only one worker would have been suspected of having lead poisoning (Table III-7). Renal biopsies taken from three of the patients demonstrated proximal tubule abnormalities with damage to the cellular mitochondria; intranuclear inclusion bodies were not found in these men.

Cramer and coworkers [126] postulated that two or three stages may be involved in the response of the human kidney to chronic lead exposure. Lead-induced nuclear inclusion bodies in the proximal renal tubular cells were thought to result from short-term exposures (less than one year). This early phase is also associated with a high urinary lead output, but no impairment of renal function occurs and cell damage is probably reversible. During the second phase (requiring at least four years of exposure) the proximal tubular cells show a decreased formation of nuclear inclusions; lead excretion is decreased and moderate interstitial fibrosis is present in the kidneys. Renal function may not be impaired, but morphological changes are considered to be irreversible. A possible third phase of lead nephropathy, characterized by renal failure, was not demonstrated by Cramer and associates [126], but nevertheless was suggested as a potential consequence from prolonged severe lead exposure. The authors stressed that diagnosis of renal dysfunction and proper staging of lead nephropathy depends on the timing of individual tests.

3. Cytogenetic Effects

Concern has recently mounted regarding the potential for lead to induce mutagenic and/or teratogenic effects in humans. However, the extrapolation of data from somatic cell studies to suggest possible effects on germ cells cannot be performed with great confidence. O'Riordan and Evans [127]

Table III-7. Initial Lead Screening and Clinical Laboratory Data (Modified from [125])

Category	Case No.	Age (yr)	Lead Exposure (yr)	Hemoglobin (g/100 ml)	Hematocrit (%)	Uric Acid (mg/100 ml)	Blood Urea Nitrogen (mg/100 ml)	Serum Creatinine (mg/100 ml)	B_{Pb} (µg/100 ml)	ALA-D (U/100 ml)	FEP (µg/100 ml)	U_{ALA} (mg/liter)	24-Hour Urine		
													Control		EDTA
													Copro (µg/day)	Pb (µg/day)	Pb (µg/day)
Normal						<7.6	<20	<1.4	<80	>120	<25	<6	<300	<200	<650
Asymptomatic renal failure (elevated blood urea nitrogen and serum creatinine)	1	28	5	9.6	28	13.2	45	2.3	48	42	29	70	757	305	5,200
Preclinical renal dysfunction (reduced glomerular filtration rate)	2	38	3	9.3	29	4.3	17	1.0	98	67	77	18	737	474	4,078
	3	39	5	14.8	42	5.7	13	1.4	51	82	64	5	7	53	1,134
	4	31	3	14.1	40	6.6	17	1.4	66	78	26	6	24	99	1,590
Normal kidney function	5	28	6	15.8	43	--	16	1.0	38	77	50	5	8	65	819
	6	49	3	15.8	45	7.6	19	0.9	52	69	138	5	20	43	530
	7	50	5	14.4	42	7.1	19	1.5	39	74	151	3	16	99	2,068
	8	34	4	15.7	47	5.8	17	1.0	29	66	71	7	127	135	976

B_{Pb} = blood lead, ALA-D = δ-aminolevulinic acid dehydratase, FEP = free erythrocyte protoporphyrin, U_{ALA} = urine δ-aminolevulinic acid, Copro = coproporphyrins.

were unable to demonstrate a significant increase over control values in the frequency of chromosome or chromatid aberrations in cultured lymphocytes taken from 35 lead workers. Blood lead concentrations among the men ranged from 40 to more than 120 μg/100 ml. More recently, however, Forni and associates [128] established a correlation between the duration of early exposure to lead and the rate of abnormal metaphases in cultured lymphocytes from 65 male workers. The incidence of abnormalities doubled after one month of exposure, increased further by two months, and remained steady up to seven months of exposure; thereafter the rate decreased somewhat. Levels of lead in the air during the study period did not exceed 800 $\mu g/m^3$; blood lead values were in the range 32 to 64 μg/100 ml. The results of Deknudt and coworkers [132] likewise confirmed that among 14 workers with symptoms of lead poisoning, an increased prevalence of chromosome abnormalities could be found. The concurrent exposure to cadmium and zinc was not thought to be correlated with the incidence of abnormalities. However, Bauchinger and associates [133] observed a group of similarly exposed workers and concluded that increased chromosome aberrations were most likely attributable to cadmium exposure. The possibility of synergistic effects cannot be ruled out.

4. Reproductive Effects

It has long been suspected that exposure to inorganic lead has an adverse effect on pregnancy, manifested as an increased incidence of stillbirths and miscarriages. Investigators have shown that transport of lead can readily occur across the placenta, such that the lead level of the newborn infant reflects that of its mother [131].

Fahim and coworkers [134] recently examined the incidence of term pregnancies with early membrane rupture and the incidence of premature

deliveries among 502 women living near lead mining regions in Missouri. Lead concentration in blood (maternal and cord) and fetal membranes were not elevated in term pregnancies. However, in term deliveries with early membrane rupture, lead concentrations were increased in blood and membrane tissues. In addition, premature deliveries were associated with higher blood levels of lead. The authors suggested a possible effect of lead on the outcome of pregnancy. The lack of a suitable control group makes these results difficult to extrapolate, however.

The reproductive ability of men was also shown to be adversely affected by "moderate" absorption of lead [135]. Concentrations of lead in blood greater than 52 μg/100 ml (groups a and b of Table III-8) were associated with a high frequency of altered spermatogenesis (Table III-9). Disorders of sexual dynamics were evident with blood lead values greater than 41 μg/100 ml (Table III-10). Among the workers with highest concentrations of lead in blood (mean, 74.50 ± 26 μg/100 ml), 75% were judged to be hypofertile, and 50% considered to be infertile. It was not possible, however, to demonstrate a reliable association between lead absorption in these men and the number of normal pregnancies per couple or the frequency of miscarriages, ectopic pregnancies, or premature births. Nevertheless, these results were interpreted to indicate that lead clearly has a direct toxic action on the male gonads at relatively low levels of absorption.

5. Developmental and Behavioral Effects

Many systematic studies with lead-poisoned children have strongly suggested an increased susceptibility to the effects of lead during the period of growth and organ development. However, documentation of lead absorption in infancy has traditionally been a major obstacle in relating exposures to effects.

Table III-8. Mean Values of Lead in Blood and Urine of Coproporphyrin and δ-ALA [135]

Group	Lead in Blood µg/100 ml	Lead in Urine µg/liter	Coproporphyrin µg/liter	δ-ALA mg/liter
A. (a) Lead-poisoned workmen, 23	74.50 ± 26	385 ± 71	394 ± 116	56.52 ± 20
(b) Lead workmen with moderately increased absorption, 42	52.80 ± 21	251 ± 106	295 ± 132	22.44 ± 8.8
(c) Lead workmen with slightly increased absorption, 35	41 ± 12	100.6 ± 41	80 ± 44	7.7 ± 4.2
B. Men with physiologic absorption of lead working in a polluted environment, 23	23 ± 14	92 ± 34	35 ± 16	4.4 ± 2.2

Table III-9. Sexual Dynamics and Decrease in Libido in Workmen [135]

Group	Libido Decrease %	Pathologic Erections %	Pathologic Ejaculation %	Orgasm Decrease %
A. (a) Lead-poisoned workmen, 23	2I	48	30	3
(b) Lead workmen with moderate increased absorption, 42	33	33	38	4
(c) Lead workmen with slight increased absorption, 35	28	22	40	5
B. Men with physiologic absorption of lead working in a polluted environment, 50	16	14	16	2

Table III-10. Frequency of Alterations in Spermatogenesis in Lead-Poisoned Workmen [135]

Group	Alterations in: Spermatogenesis No. (%)	Asthenospermia No. (%)	Hypospermia No. (%)	Teratospermia No. (%)
A. (a) Lead-poisoned workmen, 16	15 (93)	8 (50)	8 (50)	14 (86)
(b) Lead workmen with moderately increased absorption, 29	22 (68)	15 (51)	13 (44)	17 (58)
(c) Lead workmen with slightly increased absorption, 19	12 (63)	8 (42)	8 (42)	6 (31)
B. Men with physiologic absorption of lead, working in a polluted environment, 25	7 (28)	6 (24)	7 (28)	4 (16)

However, in homes with excessive water-lead levels occupied by children during the first year of life, an increased number of children were found to be mentally retarded [136]. Blood lead levels in the retarded children were higher than in non-retarded control children. The possible contribution of the mentally retarded child's mother drinking contaminated water during pregnancy must also be considered.

Blood lead values in children ranging from 40 to 80 µg/100 ml seem to be associated with adverse neuropsychological effects. Landrigan and coworkers [137] compared a group of 70 children, aged 3 to 15 years (mean blood lead 48 µg/100 ml) living near a lead smelter to a group of 78 matched controls having blood lead values under 40 µg/100 ml. They found that higher lead levels were associated with decreased intelligence and slowing in a finger-wrist tapping test. Similar results were obtained in a group of seven-year-old children who were exposed to lead between one and three years of age [138]. Persistent deficits were noted in global IQ and associative abilities, and visual motor and fine motor coordination. In addition, behavioral disturbances were evident among the lead-exposed children that were suggestive of permanent damage caused by early lead exposure. Furthermore, Baloh and coworkers [139] demonstrated a significantly increased incidence of hyperactive behavior among children with elevated blood levels (greater than 50 µg/100 ml). On the other hand, Lansdown and associates [140] saw no relationship between blood lead levels in children under 17 years of age and various measures of mental function.

Preliminary results on the effects of lead on mental functions of adult workers have shown deficits in specific areas of performance [141]. The authors suggested that increasing body burdens of lead reduce a worker's ability only during periods of high-demand performance.

IV. ANIMAL STUDIES

A. Developmental and Behavioral Effects

Exposure of the developing fetus to lead occurs by trans-placental passage from maternal sources. A number of studies with laboratory animals have confirmed this phenomenon and emphasized its importance in the pathogenesis of lead-induced abnormalities in growth and development. Green and Gruener [142] found that, in rats, a rapid equilibrium is reached between maternal and fetal blood lead concentrations. Moreover, even higher quantities of lead were transported with milk to the nursing offspring when dams were injected with inorganic lead on the day of delivery. Localization of lead in the newborn occurred primarily in the head. Kostial and Momcilović [143] confirmed these findings and noted further that the highest transport of lead in the nursing rat occurred during the late lactation period. In the golden hamster, lead nitrate (3 mg/kg; i.v.) given on day 7 or 8 of gestation crossed the placental membranes in substantial amounts within 15 minutes [144]. Thus, the permeability of the placenta to lead ions was demonstrated at low doses even during the critical period of organogenesis in this species.

Parental exposure to lead acetate has been shown to exert a detrimental effect on the subsequent learning ability of rat offspring [145]. Single parental exposure, either male or female, and dual parental exposure to lead all caused significant learning deficits. Similarly, a study has shown that rats exposed to 5 or 50 ppm of lead from conception (via maternal exposure) to adulthood resulted in delayed nervous system development [146]. As adults, the lead-exposed animals displayed hypoactivity and decreased responsiveness to the stimulatory effects of amphetamine. These results contrast with the ability of

lead to produce hyperactivity in juveniles. Additional studies conducted with rats [147, 148] and mice [149] treated neonatally with lead confirmed that growth and development are retarded, learning ability is reduced, and subtle behavioral changes result from low level exposures early in life. Lead intoxicated neonatal rats showed retardation of new cell formation in the cerebellum, with ataxia, paraplegia, and cerebellar vascular damage after three weeks of life [150].

When ewes were fed lead acetate in amounts sufficient to maintain a blood lead concentration of 34 μg/100 ml throughout gestation, learning deficits were demonstrated in their offspring [151]. Lambs from lead-exposed ewes had blood lead values of 24 μg/100 ml. Between 10 and 15 months of age these animals had reduced abilities to learn a visual discrimination task. Lambs were not affected by maternal blood concentrations of 17 μg/100 ml, which implied that a threshold for neurologic damage in the offspring of sheep may lie in that region which produces 17 to 34 μg lead/100 ml in the maternal circulation.

B. Lead Toxicity

There is considerable interest in developing a suitable animal model for lead toxicity [152]. Thus far, no one species has proven to be consistently reliable in responding to lead in a fashion analogous to humans. Consequently, the recent scientific literature contains an abundance of reports detailing specific lead-induced effects in various animals. Data derived from studies conducted with several animal species exposed to lead are summarized in Table IV-1. Taken together, these results demonstrate that the toxic effects of lead in mammals are primarily involved with damage to the hematopoietic system, the central nervous system, and the kidneys. The accumulated observations

Table IV-1. Subacute and Chronic Toxicity of Inorganic Lead

Animal	No. & Sex	Treatment	Route of Administration	Observed Effects	Reference
Rhesus monkey (newly weaned)	3 male 1 female	0.5 g lead subacetate and 1000 units vitamin D dissolved in corn oil three times a week	gastric gavage	Encephalopathy between 6 and 18 weeks; sudden ataxia, nystagmus, generalized weakness and convulsions. Urinary ALA excretion and blood lead were elevated; hemoglobin decreased. Disturbances in body weight preceded the development of encephalopathy by 2-3 weeks. The female monkey showed relative resistance to the effects of lead.	155
Rhesus monkey	4 male 4 female	lead oxide particulate (avg. 21.5 $\mu g/m^3$) 22 hours each day for 6 or 12 months	inhalation	Blood lead levels reached 17 µg/100 ml during the first few months and thereafter remained stable. Increased levels of lead found in lung, liver, kidney, and bone. No changes detected in serum chemistry or hematology; no pathologic alterations in the tissues.	156
Baboon (weaned infant)	18 Sex?	100–500 µg lead/kg/day as lead octoate or lead acetate	gelatin capsule per os	Rapid early reduction in erythrocyte ALAD activity within the first day, which remained constant for 150 days of exposure. Blood lead concentrations greater than 80 µg/100 g occurred after 75 to 100 days of exposure at 500 µg lead/kg/day as lead octoate. Results suggested that orally ingested lead is not well absorbed through the gastrointestinal tract.	157
Baboon (adult and infant)	3 female	adults: lead carbonate approx. 100 mg/kg for a total of 5 or 8 doses over a 234 day period. infant: 4 doses varying from 54 mg/kg to 357 mg/kg over an 84 day period.	intratracheal injection	Seizures observed in lead-treated adults along with generalized cerebral edema of the white matter and focal cortical necroses, probably due to epileptic convulsions. In the infant, generalized edema of the white matter was observed; the animal died on day 117.	172

Table IV-1. Subacute and Chronic Toxicity of Inorganic Lead (Cont'd)

Animal	No. & Sex	Treatment	Route of Administration	Observed Effects	Reference
Mongrel dogs (6 week-old pups)	6 Sex?	100 ppm lead as lead acetate from age 6 to 18 weeks	fed with a calcium-and-phosphorus-low purified diet	Cyclic response manifested as an initial anorexic phase (first 4 weeks) followed by an acclimatization phase (weeks 4 to 7) and a terminal debilitative cachectic stage (after consuming 191 mg lead/kg body weight). Significant anemia, leukopenia, and normoblastocytosis within 6 weeks. Also present were nonspecific serum enzyme alterations, hydropic degeneration of spermatogonia, and histopathologic changes in the liver, kidneys, and testes.	158
Beagle dogs (one year old)	12 male 12 female	100 ppm lead for 46 weeks, or 500 ppm for 30 weeks followed by 1000 ppm for 16 weeks	fed with a basic ground meal diet	Increased blood and urine lead levels, increased urinary ALA excretion, and decreased erythrocyte ALAD activity in all groups. No effect on blood regeneration (red cell count, hemoglobin, hematocrit ratio) following withdrawal of one-half the blood volume.	159
Rat (Sprague-Dawley)	36 male 36 female	lead oxide particulate (avg. 21.5 $\mu g/m^3$) 22 hours each day for 6 or 12 months	inhalation	Blood lead levels reached 28 µg/100 ml during the first few months and thereafter remained stable. Marked reduction in erythrocyte ALAD activity but no changes in levels of excreted heme precursors. No changes detected in serum chemistry or hematology; no histopathologic damage.	156
Rat (Wistar)	21 male	68.3 mg lead/day as lead acetate for 24 weeks	given as 1% lead acetate in the diet	Growth slowed by 20%. Blood lead averaged 90 µg/100 ml for the first 8 weeks and 150 µg/100 ml during weeks 11-23. Signs of hematologic alteration not evident before 8 weeks. Effects included depressed oxidative activity in reticulocytes and decreased ATPase activity in reticulocyte membranes. Results suggested a toxic action of lead on erythrocyte precursors.	160

Table IV-1. Subacute and Chronic Toxicity of Inorganic Lead (Cont'd)

Animal	No. & Sex	Treatment	Route of Administration	Observed Effects	Reference
Rat (weanling, Sprague-Dawley)	55 male	300 ppm lead as lead acetate for 6 weeks	fed with a purified diet	Significant decreases in weight gain, feed intake, and blood heme; 17.4% of the lead was absorbed and 14.7% retained. In vitro heme synthesis in blood from lead-treated animals was increased by a single injection of niacin or vitamins C plus B_{12}; pyridoxine, thiamine, and riboflavin had no effect. Excess niacin in the diet did not protect against the effects of lead on heme synthesis.	161
Rat (Wistar)	male No.?	1% or 2% lead acetate for 10 to 40 weeks	fed in the diet with 3% corn oil	Lead inclusion bodies were present in the kidneys along with some tubular swelling and vacuolar degeneration. However, renal tubular function was maintained during lead treatments. It was concluded that the rat kidney is resistant to the potential toxic effects of lead.	162
Rat (infant, Sprague-Dawley)	female No.?	20-80 ppm lead as lead acetate from 21 to 56 days of age. Prior exposure via the nursing mother given 2% lead as lead acetate	fed in the drinking water	Increased activities of renal pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose 1,6-diphosphatase, and glucose 6-phosphatase (rate-limiting enzymes involved in gluconeogenesis). Increased glucose synthesis was associated with a stimulation of the adenylate cyclase-cyclic AMP system, decreased hepatic glycogen, and decreased serum immunoreactive insulin levels.	163
Rat (4-month old, Wistar)	3 male 3 female	500 µl lead acetate solution (0.24 M lead in distilled water) every other day for a total of 5 doses	dermal; applied to shaved skin of the back	Decreased erythrocyte ALAD activity. Increased lead content in kidney, liver, and muscle, but not brain or spleen.	164
Mouse (4 weeks old, CD-1)	male No.?	0.0003 to 0.10 M lead acetate from 4 to 6 weeks of age	fed in the drinking water	Aggravation of the response to viral (RNA and DNA type) challenge, possibly by reduced interferon synthesis. Repression of the antiviral activity of interferon inducers.	165

Table IV-1. Subacute and Chronic Toxicity of Inorganic Lead (Cont'd)

Animal	No. & Sex	Treatment	Route of Administration	Observed Effects	Reference
Mouse (8 weeks old, Swiss)	14 male	2% lead subacetate for 28 days (total mean lead intake = 1.64 g)	fed in the drinking water	Incidence of pregnancy in mates of lead-treated mice greatly reduced in comparison to controls (27.6% vs. 52.7% in controls). Mutagenicity index (No. of early fetal deaths/total implants) was elevated in lead-treated mice.	166
Rabbit (New Zeland and pigmented)	14 Sex?	0.5% lead subacetate for periods up to 2 years	fed with a standard diet	Multifocal lesions of the retinal pigment epithelium and photoreceptor degeneration.	167
Pig (4 weeks old, Yorkshire)	6 Sex?	1000 ppm lead as lead acetate for 13 weeks	fed with a diet supplemented with calcium and phosphorus	Intranuclear inclusion bodies occurred in liver cord cells, renal tubular epithelium, and osteoclasts. Inhibition of osteocytic activity occurred, leading to necrosis of the osteocytes and osteoclasis. Effect was most prominent in metaphyseal trabeculae, the bone tissue with highest turnover rate. Effects were less pronounced in pigs with highest levels of dietary calcium.	168
Sheep (yearling, Columbia-Rambouilet)	20 female	4.5 and 2.5 mg metallic lead/kg/day for 6 months	fed with a supplemented diet	No signs of clinical lead poisoning or in hematology, serum chemistry, or reproductive performance. Significant differences from controls were seen in packed cell volume, hemoglobin, and alkaline phosphatase, but were not linear with lead exposure.	169
Gerbil (Mongolian)	15 male 15 female	0.125% and 0.25% lead as lead acetate for 12 weeks	fed with a ground diet	Intranuclear lead inclusion bodies in epithelial cells of the proximal convoluted tubules of the kidney were observed after 4 weeks. Cytoplasmic changes observed in proximal tubule cells containing lead inclusions were considered indicative of acute lethal injury. After 12 weeks, gerbil kidneys accumulated 4 to 6 times the amount of lead as rat kidneys.	170
Hamster (Syrian golden, 6 weeks old)	30 male 30 female	1 mg lead oxide, alone or with 1 mg benzo[a]pyrene once a week for 10 weeks	intratracheal injection	Lead oxide alone induced alveolar metaplasia (19) and adenomatous proliferation (3) in the lungs. In combination with benzo[a]pyrene, lead oxide caused adenoma (9) and adenocarcinoma (1) in the peripheral area of the lungs, as well as alveolar metaplasia (23) and adenomatous proliferation (5).	171

by numerous investigators of the toxic effects of lead in humans are in agreement with this impression. In addition, animal studies have provided evidence of lead involvement in reproductive failure [104], fetal teratogenesis [178], and cocarcinogenesis [171].

V. WORK PRACTICES AND ENGINEERING CONTROLS

Effective control of occupational exposure to lead requires the integration of proper industrial hygiene practice with adequate housekeeping, work habits, and employee personal hygiene. The hazards of lead exposure have long been recognized, and thus, protective measures have been in use for many years. Consequently, the recent literature has provided relatively little guidance in improving the occupational environment with respect to lead.

Nevertheless, VanderKolk and Schuman [153a] have recently outlined the latest opinions regarding a program of occupational lead control. Emphasis is placed on air sampling (including personal samples), engineering controls, housekeeping practices, biological testing, employment physicals, and proper work habits. In an earlier report, Hernberg [173] discussed in greater detail the factors which determine the magnitude of risk associated with various industrial situations involving potential lead exposure. Prevention of lead poisoning was logically divided into technical means of prevention (e.g., substitute chemicals, process automation, ventilation) and medical control (e.g., pre-employment examination, biological monitoring).

VI. MISCELLANEOUS

A. Chelation Therapy

In past years the administration of chelating agents to lead workers as prophylactic therapy has been employed to a limited degree. Whereas chelating agents (edetate disodium calcium, penicillamine) are generally useful in the therapy of acute lead intoxication, the value of prophylactic chelation therapy is highly questionable. In fact, a number of adverse effects can result from long-term chelation therapy.

Recent reviews on chelation therapy among workers exposed to lead conclude that the administration of chelating agents under conditions of continued exposure to lead is strongly contraindicated [71, 174]. Damage to the kidneys, increased absorption of lead from the gastrointestinal tract, and interference with metal-dependent enzymatic activity are known to occur under these circumstances. In addition, it has been noted that workers who had chelation therapy may display greater lead-induced abnormalities than those without a history of such therapy [111]. Furthermore, it was suggested that, by temporarily lowering blood lead levels, chelation therapy may nullify the diagnostic significance of elevated blood lead values while having no beneficial effect on body lead burden.

Although chelation therapy for acute lead poisoning in children is a recommended course of action [68, 119], studies with lead-intoxicated rats suggested that chelating compounds are less efficient in immature animals [175]. Other investigations with rats have shown that penicillamine did not reduce soft tissue lead, nor was it as effective as ethylenediaminetetraacetate [176, 177].

VII. SUMMARY AND CONCLUSIONS

It is apparent that occupational exposure to inorganic lead may lead to disturbances of the hematopoietic system, the central and peripheral nervous system, the reproductive system, and the kidneys. The correlation of damage in specific organs with levels of lead in the blood, however, is neither consistent nor reliable. Nevertheless, it is apparent that blood lead concentrations substantially below 80 μg/100 ml in adults are often associated with adverse effects. Thus, it is doubtful whether an industrial standard based on the maintenance of blood lead values at or below 80 μg/100 ml will be successful in the prevention of lead poisoning. Similarly, the difficulties involved in accurately predicting blood lead levels from concentrations of lead in air will prevent this parameter from being useful as the only measure of occupational hazard. On the other hand, recent studies have demonstrated a relatively good correlation between levels of erythrocyte protoporphyrins and physiologic signs of lead exposure.

Among the recent studies which demonstrated adverse physiologic effects with low-level lead exposure, reproductive failure, kidney function abnormalities, and effects on the developing fetus are of major importance. Epidemiologic investigations suggest that the prevalence of these disorders may have been underestimated in the past, or not properly attributed to lead exposure. On the other hand, retrospective studies of mortality among lead workers have failed to clearly define a lead-associated elevation in any specific cause of death. However, reported excesses of deaths in lead workers attributable to "chronic nephritis or other renal sclerosis" and "other hypertensive disease" may, in fact, have an etiological basis in lead nephropathy.

The literature on biological specimens clearly demonstrates that the microstick method for drawing capillary blood combined with any one of several microdeterminations by atomic absorption spectroscopy yields a screening procedure

comparable in accuracy and precision to the NIOSH - recommended dithizone colorimetric procedure. The micro-determinations are also superior in the number of samples which can be analyzed per day, the apparent analytical costs, and the comfort to the worker. Several analytical possibilities exist, but no one method is clearly superior. The favored choices are atomic absorption spectrometry with graphite furnace, the Delves cup system using heparinized whole blood, or carbon rod attachment using either heparinized blood, whole blood, or the punched filter paper disc method. Anodic stripping voltametry also appears a promising alternative analytical method to atomic absorption spectrometry, but few references were found to document its practical utility.

Atmospheric sampling and analysis have also been evaluated in comparison to the dithizone colorimetric procedure as recommended in the criteria document. Several methods for micro-determinations appear promising, but documentation is not as strong as with biological specimens. Atomic absorption spectrometry has two potential applications for direct analysis of grab samples: (1) analyses of filter samples collected according to the NIOSH document recommendations using carbon cup, or (2) collection using spectral grade carbon crucibles and direct AAS analyses on the crucibles. These methods, however, are not suitable for integrated time-weighted sampling. An alternative, X-ray fluorescence spectrometry, for direct analysis of sample filters, has excellent potential but does not yet appear well enough documented.

VIII. RESEARCH NEEDS

There are presently many unanswered questions regarding the dose-response parameters of lead intoxication. Major areas of uncertainty generally relate to the relationship between air lead exposure and blood lead levels, and the significance of specific blood lead values with respect to the development of potentially adverse effects. With these concerns in mind, there is obviously a pressing need for the development and validation of suitable biological monitoring techniques which can reliably predict excessive lead absorption. The emphasis in this case is on the concept of excessive absorption, as opposed to lead absorption causing alterations which may be physiologically insignificant (e.g., erythrocyte ALAD activity). In this regard, it appears that the assay of erythrocyte protoporphyrins may prove a valuable tool in the prevention of lead poisoning.

An area of great concern which has only recently received any systematic attention is the effect of lead on reproductive function and fetal development. Presently available data suggest that these processes may be among the most sensitive to the detrimental effects of lead. The significance of adverse effects on human reproduction demands the initiation of further investigation. Moreover, the effects of lead upon renal function are poorly understood and also require additional research.

It is unlikely that we will soon be able to fully evaluate the contribution of the many factors involved in lead poisoning. Thus far, it is known that dietary sources, physiological state, age, sex, and parameters of exposure conditions (e.g., solubility, particle size) are all involved in the production of lead intoxication. Properly designed studies may be able to more fully characterize these relationships, while also identifying situations where individuals may be at increased risk of poisoning.

Appendix A - Literature Search

The literature search strategy employed in preparing this update consisted of both computerized and manual techniques. Major reliance for bibliographic information was placed on a computer-generated NIOSHTIC search. In order to supplement this citation source, several steps were taken to insure that: (1) all relevant articles would be retrieved, and (2) very recent articles of relevance to the literature review would not be overlooked.

An on-line search using lead and related keywords (e.g., plumbism, pica, ALAD, protoporphyrin) was undertaken using the following data bases:

1. Chemical Abstracts (1972 to December 1976)
2. U.S. National Technical Information Service (1972 to December 1976)
3. Biological Abstracts (1972 to December 1976)
4. Science Citation Index (1972 to December 1976)
5. National Library of Medicine - TOXLINE (1973 to December 1976)

In addition to the computer-readable data bases detailed above, a manual search of Current Contents was conducted for the period November 1975 through December 1976. Pertinent articles located by manual and computer searching were examined to determine whether additional references could be located by tree searching.

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XII - Appendix V

Statement of

Edward J. Baier, Deputy Director
National Institute for Occupational Safety and Health
Center for Disease Control
Department of Health, Education, and Welfare

Before the

Department of Labor
Occupational Safety and Health Administration
Public Hearing on Occupational Lead Standard

March 1977

I welcome this opportunity to appear here today to discuss the effects of occupational lead exposure upon human health including the results of recent NIOSH studies of lead workers. With me today are the following: Dr. Kenneth Bridbord, Office of Extramural Coordination and Special Projects, Dr. Edward Baker, Bureau of Epidemiology, Dr. Theodore Thoburn, Division of Surveillance, Hazard Evaluation and Field Studies, Mr. John Bryant, Division of Physical Sciences and Engineering, and Mr. Robert Schutz, Testing and Certification Branch.

As early as the first century A.D., lead was recognized as an occupational hazard, but it was not until the 1800's, however, that systematic studies were conducted on health effects of lead exposure. Symptoms associated with excessive lead absorption have been documented in painters, printers, potters and glass workers. Exposure to excessive quantities of lead is known to have significant effects on the kidney, the peripheral and central nervous systems, and the hematopoietic system.

NIOSH estimates that more than 1 million American workers are occupationally exposed to lead. Some of the highest exposures are likely to occur in industrial processes such as primary and secondary lead smelters and lead battery operations. Lead exposure occurs in more than 100 other occupations. Relatively high exposures can be encountered in occupations such as welding, metal burning, painting and printing, and lower exposures occur among workers exposed to the

handling or combustion of gasoline containing lead additives. These occupational exposures increase the underlying body burden of lead which is derived from ambient air, food, and water. Not included in our estimates are workers exposed to lead in mining, crushing, and milling operations, for which the Department of the Interior has regulatory responsibility.

Occupational exposure to inorganic lead was high on the NIOSH list of priorities and was the subject of one of the first criteria documents we issued. The criteria document, dated in 1972 and transmitted to the Occupational Safety and Health Administration (OSHA) in January, 1973, recommended reducing the existing Federal standard for maximum lead concentration from 200 to 150 micrograms per cubic meter of air as a time weighed average (TWA) exposure for an 8-hour workday, 40-hour workweek. In August, 1975 NIOSH recommended this level be reduced below 150 ug/m^3. NIOSH felt at the time that available data were not sufficient to define precisely how much below 150 ug/m^3 the air lead concentration should be set, although a level below 50 ug/m^3 was not felt to be necessary. In October, 1975, OSHA proposed a standard of 100 ug/m^3.

There is no existing OSHA standard for maximum permissible blood lead levels. For that matter, there is no existing biological standard for any substance in the workplace. The 1972 criteria document recommended a biological standard of 80 ug per 100 grams of whole blood in adults. In 1975, NIOSH recommended reducing the maximum

permissible level to 60 ug/100 g and that level was proposed by OSHA in October 1975.

In testimony last March before the Subcommittee on Manpower, Compensation, and Health and Safety, House Committee on Education and Labor, the Director of NIOSH reviewed the occupational lead problem and also sharply criticized the routine, prophylactic use of chelating agents in workers continually exposed to lead. Since that testimony, the Food and Drug Administration circulated warnings to practicing physicians throughout the country against prophylactic chelation, and OSHA also took action against this practice. Today, NIOSH wants to reiterate its concerns about prophylactic chelation. While NIOSH believes that the use of chelating agents may be justified in acute lead intoxication, the evidence does not exist to justify their use on a prophylactic basis. A further evaluation of the chelating agent problem is being submitted for the record with this testimony.

The toxicology and metabolism of lead have been extensively studied. Inorganic lead is absorbed from the lungs and the digestive tract. Lead is transported in the blood throughout the body. Lead is stored in the bones and affects the bone marrow, causing an interference in the production of hemoglobin which can lead to anemia. The interference with the synthesis of heme causes an accumulation of heme precursors in the blood, which are useful for measuring the degree of lead intoxication, as well as the quantity of lead absorbed into the body. It is apparent from the analysis of heme precursors

that lead interferes in at least two sites in the hemoglobin synthesis pathway. At one site lead interferes with the enzyme aminolevulinic acid dehydrase (ALAD) leading to an increase of aminolevulinic acid (ALA) which can be measured in the urine. Lead interferes with the incorporation of iron into the protoporphyrin ring, resulting in an accumulation of protoporphyrins in the blood. The protoporphyrins may be measured as free erythrocyte protoporphyrin (FEP) by extraction from the red blood cells, or are measured directly in the blood in the form of zinc protoporphyrin, or ZPP. FEP and ZPP thus measure the same biological phenomenon.

In addition to the bone, lead is also stored in other vital organs and tissues including the kidneys and the nervous system. Lead can be mobilized from various storage sites and excreted from the intestinal tract and the kidneys.

Repeated exposure to lead can result in accumulation in the amount of lead stored in the body. Continued chronic exposures to high levels of lead, even intermittent, can cause death or permanent damage to the nervous system, serious damage to the kidneys and impairment of red blood cell production. Once the kidneys are damaged by lead, the ability of the body to excrete lead through the kidneys is impaired, thus making lead in urine a poor screening test for lead absorption.

Workers exposed to excessive levels of lead may feel weak, tired, and irritable. They may experience trembling, severe colic and digestive disturbances, and convulsions. A characteristic sign of severe lead poisoning is "wrist drop", caused by damage to the nerves controlling the extensor muscles of the forearm, wrist and fingers.

Of considerable concern are the effects resulting from long-term lead exposure. There is evidence that prolonged exposure can increase the risk of nephritis, mental deficiency, premature aging, and high blood pressure.

Another category of adverse effects includes the so-called "subclinical" changes produced by lower exposures to lead. These changes are generally measured only by laboratory tests and would not necessarily be evident by routine physical examination. These workers may have early damage to the nervous system, muscular weakness, behavorial disturbances, and interference with red blood cell production. The use of the term "subclinical", however, does not mean that these changes are without significance from a health point of view.

One of the most frequently measured of these "subclinical" changes is the excretion of ALA in the urine. Increased excretion of ALA in the urine is observed in workers as blood lead levels rise above 40 to 50 ug/100 g. A report by a National Academy of Science committee studying the effects of airborne lead concluded that this

increased excretion is significant. Another National Academy of Science committee, this time studying the effects of lead poisoning in children, concluded that . . . ."environmental limits set to prevent reversible effects in the hematopoietic system should serve to prevent potentially irreversible effects in the nervous system."

Perhaps the most frequently employed measure of lead absorption into the body is the quantity of lead in the blood. Most clinical measures of lead toxicity have been related to blood lead measurements. One of the greatest difficulties with the measurement of blood leads is the high level of skill required in analytical techniques and the great care demanded to avoid the risk of sample contamination by lead or of lead loss. The proficiency record of laboratories in blood lead determinations has at times been less than adequate as shown by a recently completed Center for Disease Control (CDC) study of commercial clinical laboratories. It was disturbing to find that only one-third of all commercial laboratories in this study performed acceptably, but it is encouraging that in another CDC proficiency testing survey about two-thirds of State and public laboratories did perform well. A copy of the commercial laboratory proficiency testing study is being submitted for the hearing record. The poor record of commercial laboratories on blood lead testing is but one of the reasons why NIOSH opposses setting an occupational lead standard based solely upon blood lead levels.

In contrast to blood lead, the ZPP test offers certain advantages. For example, ZPP is a relatively stable indicator reflecting lead absorption over a several month period; ZPP does not suffer from problems of lead contamination or lead loss; and ZPP provides an index not only of lead absorption, but also of lead effect. A major advantage of the ZPP test is that rapid, reliable and economic instruments are available which allow instantaneous readout of ZPP tests following finger stick blood specimens. One of the major problems with ZPP is that this is a very recently developed test and only limited data are available on blood lead-ZPP correlations. Further, ZPP may present calibration problems, and careful attention must also be given to quality control procedures. Under these circumstances, it would seem wise to develop a biologic screening approach which incorporates ZPP or an equivalent screening test with blood lead determinations. Provisions for biologic monitoring must, however, be accompanied by specific quality control requirements.

Another reason why NIOSH opposes setting an occupational standard based solely on biologic monitoring is that this would discourage the development and implementation of adequate engineering controls and would place undue reliance upon personal protective equipment such as respirators. NIOSH believes it is necessary to reiterate its basic recommendation that employee exposure should be reduced to the lowest possible level by use of engineering controls. Respirators may be used to protect employees while engineering controls are being installed or to temporarily supplement such controls. NIOSH does not

recommend continual respirator use as the primary method of controlling any employee's exposure. Respirators must be regarded as temporary solutions to problems or as devices available for emergency respiratory protection, not as permanent answers to employee exposure. A list of respirator requirements for the lead standard is being submitted for the record.

NIOSH endorses the concept of an occupational standard for lead which includes provisions for both environmental and biological monitoring. For example, air lead determinations can help to prevent excess lead absorption. The principal advantage of an air lead determination is to prevent excessive exposure. Since lead is absorbed by routes in addition to inhalation, a biological measure of lead absorption is necessary.

NIOSH's concern about the lead problem is evidenced by our continuing research and health hazard evaluations and other activities in lead operations. NIOSH is currently updating the lead criteria document. NIOSH and the Bureau of Epidemiology, Center for Disease Control (CDC), have conducted comprehensive occupational surveys of lead exposure at primary and secondary lead smelters. The largest of these studies, undertaken in response to requests by union representatives and state health officials, was conducted at a primary lead smelter at Kellogg, Idaho, and involved about 500 workers. Within approximately the last year NIOSH-CDC has examined nearly 1,000 workers occupationally exposed to lead, including those at Kellogg.

An interim report of our results from certain aspects of the Kellogg study is being submitted for the record as are results from other recently completed NIOSH-CDC lead studies. These studies included investigations at a secondary lead smelter in Memphis, Tennessee; a lead chemicals plant in Joplin, Missouri; a secondary lead smelter in Salt Lake City, Utah; a secondary lead smelter in Eagen, Minnesota, and a secondary lead smelter in Atlanta, Georgia. In addition, NIOSH has also supported other lead studies such as the investigation of a secondary lead smelter at Vernon, California, to be presented later at these hearings by scientists at the Mount Sinal School of Medicine. This study is being submitted for the record by NIOSH.

Among the major findings of our studies are the following:

First, epidemiologic studies of workers at 5 different lead plants across the U.S. have shown unacceptably high blood lead levels and symptoms of lead poisoning in every plant studied. Hematologic, neurologic, and renal damage due to lead were also encountered. Inappropriate medical practices were noted including the misuse of oral chelating drugs and the allowing of lead-poisoned workers to continue to be exposed to lead during chelation therapy.

Second, the usefulness of monitoring blood lead and/or protoporphyrin levels as indicators of lead toxicity was clearly shown by the high degree of correlation between these measurements and the

signs and symptoms of lead toxicity. The newly developed portable method of zinc protoporphyrin (ZPP) determination has been shown to be a promising method of screening lead-exposed workers.

Third, in several locations, home contamination with lead dust from lead plants resulted in increased lead absorption among workers' children; and in one location several cases of lead poisoning were observed. These studies illustrate the importance of good work practices such as not bringing contaminated work clothes and shoes home and showering before going home, and other practices minimizing exposure to the worker and to his or her family.

Fourth, chronic neurologic and renal effects of lead exposure were demonstrated in our studies. Neuropathy was noted at a relatively low blood lead level (81ug/100 ml) and after only 2 months of exposure. Abnormal glomerular function (elevated blood urea nitrogen and creatinine levels and decreased glomerular filtration rates) and abnormal tubular function (impaired urinary concentrating ability and reduced lead clearance rates) were noted in lead workers. These studies clearly demonstrated an increase in symptoms compatible with lead intoxication and a decrease in hemoglobin concentrations as blood lead levels rise above 60 ug/100 ml.

These findings emphasize the need for improved industrial hygiene measures in the lead industry and the importance of biological monitoring in preventing lead toxicity. Based on the data contained

in these studies, a blood lead standard no higher than 60 ug/100 ml is recommended. These data clearly establish the need to reduce the maximum blood lead levels for an individual worker from 80 ug/100 ml to 60 ug/100 ml. A blood lead level of 60 ug/100 ml is equivalent to a blood lead level of 57 ug/100 g, but this difference is well within the analytic variability for blood lead determinations. The decreased urinary lead excretion observed in workers with evidence of kidney damage argues against the retention of urinary lead as a screening test.

The results from these studies demonstrate that workers in this country are being exposed to high concentrations of lead in the air and are absorbing dangerous amounts of lead into their bodies. This is occurring despite the fact that hazards of lead exposure are well recognized and technology to reduce these hazards is, in our opinion, available.

This situation clearly demonstrates the inadequacy of current OSHA compliance programs aimed at reducing lead exposure. Data on lead compliance activities supplied to us from OSHA further confirm the inadequate enforcement of the existing lead standard. The fact that these compliance programs are inadequate reflects a lack of vigorous enforcement of the existing lead standard, not a lack of knowledge of how to control the lead hazard.

Data supplied to us from General Motors involving a lead battery plant at Muncie, Indiana, clearly demonstrate what can be done to control lead exposure at an older battery plant. The majority of departments tested at this plant had average air lead exposures during 1976 below 100 ug/m^3 based upon personal monitors. Blood lead levels in over 90% of the workers were 60 ug/100 ml or lower. Average exposures at this plant using personal monitors were below 100 ug/m^3 in the assembly areas and below 150 ug/m^3 in the oxide pasting and grid casting areas.

If blood lead levels are used as criteria for technical feasibility, the data reported recently from Finland are especially encouraging. Assuming that keeping 90% or more of individual blood lead levels at 60 ug/100 g or lower is a good indication of technical feasibility to meet a 100 ug/m^3 standard and, assumbing that respirators were not generally used in these industries, then, the following industries or operations in Finland have clearly demonstrated such feasibility: crystal glass manufacturing, car radiator repair, lead glazing, cable manufacturing, scrap metal shop work, car repair, machine shop work, aluminum manufacturing, sheet metal work, paint manufacturing, shipbuilding, iron and steel founding, painting, service station work, plumbing, manufacturing electric lamps, telephone repair and installation, manufacturing radio and telephone equipment, and traffic police work.

The Finnish experience also confirms what is generally known in the United States, i.e., that lead scrap smelting and storage battery manufacturing present significant problems with respect to lead absorption, but not problems which are insurmountable.

One of the important issues to be considered at this hearing involves the relationship between exposure to lead in air and absorption of lead into the body, measured in terms of blood lead level. The OSHA proposal concluded that in order to keep blood lead levels in individual workers below 60 ug/100 g, air lead levels would have to be reduced below 100 ug/m^3, caculated as an 8-hour time weighed average, 40-hour workweek. The data available to NIOSH generally support this conclusion.

The basis for our agreement with this earlier assessment is spelled out in two attachments to this testimony. One attachment reviews the published studies relating blood lead levels to air lead exposure covering primarily the equivalent occupational exposure range up to 50 ug/m^3. This assessment, based on about 10 studies, concluded that to keep blood lead levels in male workers below 40 ug/100 g, air lead exposures have to be kept under 50 ug/m^3. An additional observation from the general population is that men have higher blood lead levels than women with comparable environmental exposures. The reason for this is not clearly understood. The second assessment involves an extensive analysis of air lead and blood lead data at the General Motors battery plant at Muncie. These important data indicate

that a good correlation exists between air lead exposure (especially when based on personal samplers) and blood lead over a range of air leads up to about 200 ug/m^3. These data further indicate that if yearly average personal sampler air lead exposure in a department is kept below 100 ug/m^3, yearly average blood leads in over 90% of workers will be under 60 ug/100 ml. Similarly, if yearly average personal sampler air leads in a department are kept under 50 ug/m^3, yearly average blood leads will be 40 ug/100 ml or lower over half of the workers. One of the greatest impacts of reducing lead exposure in air from 200 to 100 ug/m^3 is a great increase in the number of workers with blood lead levels 40 ug/100 ml or lower.

In reviewing the relationship between air lead exposure and blood lead level, it is also apparent that a linear relationship between air lead and blood lead does not occur over the whole range of exposures. Incremental changes in air lead exposure in the range up to 100 ug/m^3 produce greater increases in blood lead than do similar increases in the range from 100-200 ug/m^3.

A problem of special significance in setting a lead standard, in part because of our national commitment to equal employment opportunity, is the concern for female employees of childbearing age. Lead absorbed in the bloodstream of pregnant women can cross the placenta and enter the blood of the fetus where it may cause neurologic damage to the child. Lead is also found in mothers' milk. Other special concerns are susceptible workers known to have certain

clinical conditions such as kidney problems, neurologic disorders, and anemias. Enzyme disorders and inherited hemoglobin abnormalities may also pose a similar problem.

Adequate data do not currently exist to estimate what percentage of the workforce is made up of individuals with increased susceptibility to lead intoxication. Blood lead levels required to adequately protect susceptible individuals are not well established. The fact that certain individuals may be more susceptible to lead effects is an argument for setting a blood lead standard to protect against early biochemical changes induced by lead. Protecting against these earlier changes will hopefully assure protection against the more serious and potentially irreversible lead effects, even in susceptible individuals. Women show early abnormalities in heme synthesis at lower blood leads than men, and show greater abnormalities in heme synthesis at the same blood lead level as men. Conversely, women in the general population tend to have lower blood lead levels than men exposed to similar environmental levels. NIOSH does not believe that adequate data exist to fully evaluate whether women per se are more susceptible than men to lead effects.

The real issue of susceptibility to lead and women involves effects of lead upon the fetus. NIOSH does not recommend that women of childbearing age be excluded from work involving exposure to lead, but NIOSH does recommend that present and future lead standards be

vigorously enforced as one way to provide additional protection to the fetus.

The issues of lead reproductive effects on men, as well as women, chromosomal damage, and lead carcinogenicity were discussed in a recent Department of Health, Education and Welfare report dealing with human health consequences due to lead exposure from automobile emissions. A copy of this report is being submitted for the record. The data on chromosomal damage among workers occupationally exposed to lead provide contradictory results, and no clearcut conclusions can be drawn. The data on carcinogenicity are also not substantial enough to consider lead a human carcinogen, although lead remains a suspect carcinogen based upon limited animal data. Further studies could, of course, change this conclusion.

Historic data involving undoubtedly very high exposures document that lead compounds can be used as abortifacients and that women occupationally exposed to lead have increased miscarriage rates. Lead is known to cross the placenta and lead concentrations in maternal blood and fetal/newborn blood correlate with each other, with newborn blood lead levels being somewhat lower. Recent studies have shown that blood lead levels between 50 and 80 ug/100 ml are associated with diminished fertility of male workers based upon analysis of sperm. What is not clear, is precisely the level of blood lead in the mother or father which would protect against lead effects in the newborn, including those involving the nervous system. Limited data in

experimental animals suggest that blood lead levels in the 35 to 45 ug/100 g range at birth may be associated with subtle neurologic damage. Data from young children suggest that the risk of neurologic damage increases as blood lead levels rise above 40 ug/100 g. Among the factors which make extrapolation of these data to precise standards difficult are the relative hemoconcentration of the newborn, the relative hemodilution of the pregnant woman and the possibility, not proven, of mobilization of lead from the skeleton during pregnancy. The fact that a nursing infant can be exposed to lead via mother's milk is an additional complicating factor.

The existence of potentially susceptible groups to lead, the possibility of damage to the fetus at blood lead levels in the 30 to 40 ug/100 g range and the possibility of damage to male germ cells at blood lead levels of about 50 ug/100 ml present difficult questions in recommending biologic standards for lead absorption.

Studies suggesting the need for establishing a blood lead standard at less than 60 ug/100 g would place considerable emphasis upon a limited number of observations which have not been confirmed by multiple investigators. To do this would place the recommendation of a blood lead level in the workplace on less firm ground than if NIOSH continued to endorse a blood lead maximum of 60 ug/100 g. The opinion of the Institute is to adhere to its earlier recommendation, i.e., 60 ug/100 g particularly since recent studies clearly support the need to reduce blood lead levels from 80 to 60 ug/100 g.

In adhering to the 60 ug/100 g figure, NIOSH has not relinquished its concern for possible effects that may occur below 60 ug/100 g. Adherence to this 60 ug/100 g figure should not be interpreted as firm NIOSH opposition to establishing a lower blood lead standard. In fact, NIOSH endorses a lower blood lead standard as a future goal to provide greater assurances of safety. The OSHA proposal would establish an action level of 50 ug/m^3 for lead in air. As noted above, exposures of 50 ug/m^3 or less would keep blood lead levels in virtually all workers at about 40 ug/100 g or lower. This should protect against "subclinical" effects of lead including the hematopoietic system and against other potential effects of lead as noted above. For workers exposed above the action level but below the maximum air lead level of 100 ug/m^3, NIOSH endorses a vigorous medical surveillance program involving, for example, ZPP testing or other screening tests to identify workers with blood lead levels of 40 ug/100 g or higher. This 40 ug/100 g figure corresponds to a biological "action level". Workers with blood lead levels of 40 ug/100 g or higher should have periodic medical exams to identify, as early as possible, any adverse effects which may occur. Such a program of medical surveillance will also help to identify workers who may be highly susceptible to lead effects. NIOSH estimates that even at the proposed air standard of 100 ug/m , less than half of the workers will have blood lead levels above 40/100 g.

Before closing our formal presentation, I should like to list the additional information which NIOSH is now submitting for the record.

Letter from Director, NIOSH to Acting Deputy Assistant Secretary, OSHA, August 4, 1975.

A report of recent medical studies of five U.S. lead plants.

Initial report of an investigation of employees of a secondary lead smelter in Vernon, California.

Interim report on analysis of blood and air lead data from General Motors, Delco Battery Plant, Muncie, Indiana.

A report on the relationship between air lead exposure and blood lead levels in occupational situations.

Summary report on proficiency testing of blood lead, 1976.

A review of the recent literature concerning the relationship of free erythrocyte protoporphyrin, zinc protoporphyrin and blood lead level.

A review of prophylactic chelation therapy in occupational lead poisoning.

Recommendations for respirator selection.

Follow-up of a health hazard evaluation, involving lead exposure and kidney disease.

Supplemental information on sampling and analytic procedures and engineering control technology.

Interim report on Bunker Hill Study.

Report on human health consequences due to lead exposure from automobile emissions.

Recommendations for the prevention of lead poisoning in children.*

We are now ready to respond to questions concerning our prepared remarks or the backup material submitted for the record.

*A copy of these above listed attachments to the testimony may be obtained from the National Technical Information Service, Springfield, Virginia 22161, PB281735/AS.

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