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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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 1×10^{-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 Copro (µg/day)	24-Hour Urine: Control Pb (µg/day)	24-Hour Urine: EDTA 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	21	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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