

<u>Category</u>	<u>Observed Effect</u>
Adverse:	Symptoms may continue during therapy in at least some workers.
	Increased absorption of lead from the gastrointestinal tract when given orally.
	Imbalance in metabolism of metals other than lead.
	Electrocardiograph changes.
	Return of symptoms following chelation.
	Temporary elevated blood lead level during treatment.
	Therapy associated with kidney damage (rare).

D. REVERSIBILITY

The majority of the effects of lead on the body are reversible with time. Exceptions are the rare changes in kidney structure and function which appear as a late sequelae to heavy lead exposures in adults, and the decreased cerebral function which accompanies prolonged and high exposures in children. Once symptoms have cleared and the body burden has dropped as measured by concentrations of lead in the blood of 40 ug/dL or less there are no reasons that the employee cannot return to further work in the lead trades.

E. PREVENTION

1. Selection. Prevention of acquiring health effects from working with lead commences with selection. In order to minimize adverse effects, workers should not be placed at exposure if they have increased risk to themselves because of:

- (a) previous history of diseases of the kidney;
- (b) evidence of current kidney disease;
- (c) anemia, abnormal hemoglobins;
- (d) past or present evidence of neurologic disease or emotional disorders;
- (e) present increased body burden;
- (f) undue concern regarding lead intoxication;
- (g) history of childhood lead poisoning.

N 27034

2. Environmental Controls

- (a) Isolate the more hazardous operations from the general plant area. House them in a room by themselves;
- (b) Enclose lead-containing vessels, whenever possible, to prevent the escape of fumes;
- (d) Always remove dust at the source by means of local exhaust ventilation, or by enclosed discharge and collection system;
- (e) Do not let fumes circulate through the plant. Extract them at their origin by means of air-cleaning systems whenever possible.
- (f) When transporting, mixing, or feeding lead-bearing materials into vessels:
 - o Take steps to prevent spillage.
 - o Dampen any dry, powdery materials, whenever possible, to prevent them from becoming airborne.
- (g) NEVER DRY-SWEEP THE FLOOR. If dust, or other lead-bearing materials, collect on the floor, always try to use vacuum scrubbers to clean up, whenever plant design and housekeeping permit it.
- (h) Dispose of lead-bearing waste in an environmentally acceptable manner.
- (i) Don't create dust clouds by poor work practices, such as clapping together contaminated objects or clothing.

3. Counseling. All employees should have the right to know all information concerning the toxicity of the material with which they work and the hazards of the job. This is best done by individual counseling, though group sessions will suffice. The employee should be advised as to the results of his biologic monitoring, the results of air monitoring, the results of their medical examination including any health problems both related and not related to their work, and their right to a second medical opinion. Finally a copy of the Lead Standard of 1978 and its appendices should be made available at their request.

4. Personal protective devices. All necessary protective devices are to be furnished by the employer such as coveralls, gloves, hats, shoes, disposable coverlets, face shields, vented goggles, and respirators.

5. Personal hygiene. Encouragement of the practice of good hygiene is the responsibility of the supervisor which should be augmented by safety and health personnel. The major points to be emphasized are:

- (a) Always washing hands before eating or smoking; never putting hands in the mouth;
- (b) not smoking in plant or if done then only in "clean" areas;
- (c) eating only in a clean lunchroom;
- (d) avoiding touching lips and nostrils;
- (e) avoiding rubbing clothing against the face;
- (f) avoiding inhaling plant smoke.

6. Clean lunch facilities. A clean lunch room apart from the lead-processing area should be made available. Wash-up areas should be near by. Continual clean up of the lunch space is mandatory.

7. Check on work practices. When ever the PbB increases significantly or exceeds the level of 50ug/dL, the employee's work practices should be reviewed by the supervisor and safety engineer or industrial hygienist.

8. Examinations. Times of performance physical examination, including histories and laboratory work, are to be offered the employee:

- (a) at least annually when the blood lead exceeds 40 ug/dL anytime during the preceding 12 months;
- (b) prior to the first assignment of an employee to an area in which the concentration of lead is at or exceeds the action level;
- (c) when the employee develops signs or symptoms compatible with lead intoxication;
- (d) employee seeks advice concerning the effect of their past or present exposure on the employee's ability to procreate a healthy child;
- (e) when the employee has demonstrated difficulty in breathing during a respiratory fitting test;
- (f) upon medical removal;
- (g) returning to work after medical removal.

The content of the examination will include:

- (a) a detailed work history and a medical history, with particular attention to past lead exposure (occupational and non-occupational), personal habits (smoking, hygiene), and past gastrointestinal, hematologic, renal, cardiovascular, reproductive and neurological problems;
- (b) a thorough physical examination, with particular attention to teeth, gums, hematologic, gastrointestinal, renal, cardiovascular, and neurological systems. Pulmonary status should be evaluated if respiratory protection will be used;
- (c) a blood pressure measurement;
- (d) a blood sample and analysis which determines: (1) Blood lead level; (2) Hemoglobin and hematocrit determinations, morphology; (3) Zinc protoporphyrin; (4) Blood urea nitrogen; and, (5) Serum creatinine;
- (e) routine urinalysis with microscopic examination; and
- (f) any laboratory or other test which the examining physician deems necessary by sound medical practice.

Who does the examinations? A person competent to do so, under the supervision of a licensed physician.

With What Should the Examined be Provided?

- (a) A copy of the OSHA regulation for lead including all Appendices;
- (b) A description of the affected employee's duties as they relate to the employee's exposure;
- (c) The employee's exposure level or anticipated exposure level to lead and to any other toxic substance (if applicable);
- (d) A description of any personal protective equipment used or to be used;
- (e) Prior blood lead determinations; and
- (f) All prior written medical opinions concerning the employee in the employer's possession or control.

9. Removal. Based on:

- (a) PbB at or >50ug/dL average of last 3 samples or six months' average;

- (b) final medical opinion as to detection of medical condition placing employee at material impairment to health from exposure to lead;
- (c) pending a final medical opinion,
- (d) employee voluntarily may remove.

10. Prevention of further exposures. Work at low lead job where concentration of lead in the air is below the PEL; restrict from further work with lead.

VII. COMPLIANCE WITH OSHA STANDARDS

1. SUMMARY OF PROVISIONS OF OSHA LEAD STANDARD

EXPOSURE LIMIT

50 UG/M³

EXPOSURE MONITORING

REPRESENTATIVE OF ALL JOBS

RESPIRATORY PROTECTION

REQUIRED WHEN AIR CONCENTRATION
IS > 50 UG/M³
TIME OF WEARING < 4.5 HRS.
NIOSH/MESA APPROVED

PROTECTIVE CLOTHING AND
EQUIPMENT

MINIMUM OF COVERALLS, GLOVES,
SHOES

HOUSEKEEPING

SURFACES AS FREE AS POSSIBLE OF
LEAD (NO CLEANING WITH
COMPRESSED AIR)

HYGIENE FACILITIES

SUITABLE CHANGE ROOMS, LAVATORIES,
SHOWERS, CLEAN ROOM, LUNCH ROOM

MEDICAL SURVEILLANCE

AT LEAST ANNUAL

ADVISE TO EMPLOYEE AS TO:

ON REQUEST

UNUSUAL MEDICAL FINDING

PRIOR TO REASSIGNMENT

CONDITIONS PLACING THEM AT
INCREASED RISK OF IMPAIRMENT
TO HEALTH

AS MEDICALLY APPROPRIATE

SPECIAL PROTECTIVE MEASURE
REQUEST.

MATERIAL TO BE GIVEN M.D.
BEFORE EXAMINATION

LIMITATION AS TO USE OF
RESPIRATORS

PROVIDE OSHA STANDARD TO
PHYSICIAN

RESULTS OF BLOOD LEAD VALUES

EMPLOYEES EXPOSURE LEVEL
TO LEAD AND OTHER TOXICANTS

MEDICAL CONDITIONS REQUIRING
FURTHER DIAGNOSIS OR
TREATMENT

PRIOR MEDICAL OPINIONS

PRIOR BLOOD LEAD MONITORING
DATA

CHELATION

PROPHYLACTIC CHELATION FORBIDDEN

MEDICAL REMOVAL PROTECTION

PROVISION TO TRANSFER
(AREA < UG/M^3) OR LAYOFF
RETURN AFTER BLOOD LEVEL
REACHES UG/dL

TRAINING

PROVISION OF INFORMATION
CONCERNING LEAD

POSTING OF WARNING SIGNS

AREAS WHERE PEL IS EXCEEDED

RECORDKEEPING

MAINTAIN AIR MONITORING, BIOLOGIC
MONITORING AND MEDICAL
RECORDS FOR 10 YEARS

MEDICAL REMOVAL RECORDS
(DURATION OF EMPLOYEE'S
EMPLOYMENT AT THAT
WORKPLACE).

AVAILABILITY OF RECORDS:
EMPLOYEES, FORMER EMPLOYEES
AND AUTHORIZED REPRESENTATIVES.

2. Other Federal Statutes Important to the Industry

The following is a summary of the most important federal statutes concerned in whole or in part with the regulation of toxic substances.

CLEAN AIR ACT. The Clean Air Act is administered by the EPA. Although the principal enforcement provisions are the responsibility of local governments, overall administrative responsibility rests with the EPA. This act requires criteria documents for air pollutants and sets both national air quality standards and standards for sources that create air pollutants, such as motor vehicles, power plants, etc. Important actions taken under this law include standards for a phased-out elimination of lead in gasoline and the setting of sulfuric acid air emission guidelines for existing industrial plants.

CLEAN WATER ACT. (Amends *Federal Water Pollution Control Act*) Also administered by the EPA, the Clean Water Act provides for funding of municipal sewage treatment plants but, with respect to toxicity prevention, it is more important that it regulates emissions from municipal and industrial sources. Some of the more important actions taken under this statute include setting standards for emissions of inorganics from smelter operations and publishing priority lists of toxic pollutants. This act allows the federal government to recover clean-up and other costs as damages from the polluting agency, company, or individual.

CONSUMER PRODUCTS SAFETY ACT (AND CONSUMER PRODUCTS SAFETY COMMISSION IMPROVEMENTS ACT). Administered by a Consumer Products Safety Commission, the Consumer Products Safety Act is designed to protect the public against risk of injury from consumer products and to set safety standards for such products.

CONTROLLED SUBSTANCES ACT. The Controlled Substances Act not only strengthens law enforcement in the field of drug abuse but also provides for research into the prevention and treatment of drug abuse.

FEDERAL FOOD, DRUG AND COSMETIC ACT. The Federal Food, Drug and Cosmetic Act is administered by the Food and Drug Administration (FDA). It establishes limits for food additives and cosmetic components, sets criteria for

drug safety for both human and animal use and requires the manufacturer to prove both safety and efficacy. The FDA is authorized to define the required toxicity testing for each product. This act contains the Delaney clause, which states that food additives that cause cancer in humans or animals at any level shall not be considered safe and are, therefore, prohibited from such use. This law also empowers the FDA to establish and modify the generally recognized as safe list (GRAS) and to establish good laboratory practice (GLP) rules.

FEDERAL INSECTICIDE, FUNGICIDE AND RODENTICIDE ACT (FIFRA). Administered by the EPA, this act regulates all pesticides (and other agricultural chemicals, such as plant growth regulators) used in the United States. It includes registration requirements, with appropriate chemical and toxicological tests prescribed by the agency. This act also permits the agency to specify labels, to restrict application to certified applicators and to deny, rescind, or modify registration. Under this act, the EPA also establishes tolerances for residues on raw agricultural products.

OCCUPATIONAL SAFETY AND HEALTH ACT. Administered by the Occupational Safety and Health Administration (OSHA), the Occupation Safety and Health Act concerns health and safety in the workplace. OSHA sets standards for worker exposure to specific chemicals, for air concentration values, and for monitoring procedures. Construction and environmental controls also come under this act. It also provides for research, information, education, and training in occupational safety and health. By establishing NIOSH (National Institute for Occupational Safety and Health) the act provided for appropriate studies to be conducted so that regulatory decisions could be based on the best available information.

NATIONAL ENVIRONMENTAL POLICY ACT. The National Environmental Policy Act is an umbrella act covering all US government agencies, requiring them to prepare environmental impact statements for all federal actions affecting the quality of the human environment. Environmental impact statements must include not only an assessment of the effect of the proposed action on the environment but also alternatives to the proposed action, the relationship between local short-term use and enhancements of long-term productivity, and a statement of irreversible commitment of resources.

This act also created the Council on Environmental Quality, which acts in an advisory capacity to the president on matters affecting or promoting environmental quality.

RESOURCE CONSERVATION AND RECOVERY ACT. Also administered by the EPA, the Resource Conservation and Recovery Act is the most important act governing the disposal of hazardous wastes; it promulgates standards for identification of hazardous wastes, their transportation, and their disposal. Included in the latter are siting and construction criteria for landfills and other disposal facilities as well as the regulation of owners and operators of such facilities.

TOXIC SUBSTANCES CONTROL ACT. Administered by the EPA, the Toxic Substances Control Act is mammoth, covering almost all chemicals manufactured in the United States for industrial and other purposes, excluding certain com-

VIII A

Gerhardsson, L., & Lundstrom, N.G.
Mortality and lead exposure: a retrospective cohort
study of Swedish smelter workers.
British Journal of Industrial Medicine, 1986, Oct.,
43(10):707-712.

The study is based on the work histories and mortality data for 3832 male workers first employed before 1957 at a copper smelter in northern Sweden and followed up from 1950-1981. From the 3832 workers, a lead cohort consisting of 437 workers employed for at least three years at sites with considerable lead exposure during 1950-74 was selected. These workers had regularly had blood lead measurements performed since 1950. Based on the cumulative blood lead dose 1950-74 and peak blood lead values, the cohort was subdivided into high mean, low mean, high peak and low peak groups. Standardized mortality ratios (SMRs) were calculated for the six groups using general and local reference populations. The original cohort of 3832 workers showed considerable excess of deaths for total mortality, malignant neoplasms, especially lung and stomach cancer, ischaemic heart diseases and cerebrovascular diseases when compared with the general population. In the lead cohort where the workers had been subjected to a considerable lead exposure, only the raised SMR for lung cancer was sustained (SMR = 152, not significant). No significant differences were found between high lead and low lead exposed smelter workers.

IX
A Position Paper

Mushak P; Davis JM; Crocett AF; Grant LD.
Prenatal and postnatal effects of low-level lead exposure: integrated summary of a report to the U.S. Congress on childhood lead poisoning.
Environmental Research, 1989 Oct, 50(1): 11-36.

This article provides an integrated summary of a report to Congress from the Federal government (ATSDR) on childhood lead poisoning in the United States, with particular reference to low-level lead exposure and its effects on the fetus and the preschool child. As mandated by Section 118(f)(1)(C) of the 1986 Superfund Amendments and Reauthorization Act (SARA), ASTOR has examined the full spectrum of human in utero and postnatal lead toxicity, with emphasis on low-level neurotoxicity and adverse impacts on growth indices in risk populations. Especially important has been assessment of the relative persistence of these effects in later life as discernible from a number of longitudinal studies now underway around the world. Included in the Congressional report were discussions of dose-effect and dose-response relationships using blood lead levels as the indicator of lead dose.

IX B

Kopp SJ; Barron JT; Tow JP.
Cardiovascular actions of lead and relationship to
hypertension: a review.
Environmental Health Perspectives, 1988 Jun, 78: 91-
99.

Chronic and acute lead poisoning cause overt, clinical symptoms of cardiac and vascular damage with potentially lethal consequences. Morphological, biochemical, and functional derangements of the heart have all been described in patients following exposure to excessive lead levels. Disturbances in cardiac electrical and mechanical activity and postmortem evidence of morphological and biochemical derangements of the myocardium have all been reported following excessive exposure to lead in humans. In addition, signs of vascular degeneration, abnormal vascular smooth muscle function, and altered vessel compliance have been described in humans chronically and acutely exposed to toxic lead levels. Similar cardiovascular complications have been detected following excessive lead exposure in experimental animals. Myocarditis, electrocardiographic disturbances, heightened catecholamine arrhythmogenicity, altered myocardial contractile responsiveness to inotropic stimulation, degenerative structural and biochemical changes affecting the musculature of the heart and vasculature, hypertension, hypercholesterolemia, atherosclerosis, and increased vascular reactivity to alpha-adrenergic agonists have been among the reported cardiovascular disturbances linked to lead poisoning. Less certain are the cardiovascular effects of subclinical lead poisoning. Although controversial, chronic low-level lead exposure has been linked to hypertension and other cardiovascular disturbances in both clinical and experimental studies. In general, it can be concluded that lead over a wide range of exposure intensities can induce significant changes in the function of the cardiovascular system. Evidence points to the involvement of multiple sites of action. Cardiac and vascular sites, as well as sites within the central nervous system, have all been implicated in the sequelae of cardiovascular effects. The exact pathogenic mechanisms that underline the actions of lead in the cardiovascular system, however, have yet to be elucidated definitively. (Abstract truncated at 250 words)

Bushness PJ; Jaeger RJ.

Hazards to health from environmental lead exposure: a review of recent literature.

Veterinary and Human Toxicology, 1986 Jun, 28(3): 256-261.

There are adequate demonstrations of the adult and pediatric health risks associated with lead exposure. This document presents the scientific facts surrounding human health effects as well as providing an interpretation of some of the animal toxicology studies. There are numerous circumstances where economic and societal pressures have resulted in the continued use of materials that are potentially toxic, hazardous and injurious to the public health and welfare. While declining, the present use of lead in gasoline and its airborne release from smelting and metal refining industries located near metropolitan centers is no exception. The demonstration that continued lead exposure from airborne sources results in intellectual deficiency should be sufficient to result in the mobilization of public health resources and the minimization or elimination, if necessary, of such hazards to the public welfare. Based on this review, this is the position that is suggested by the authors of this document.

Ehle AL; McKee DC

Neuropsychological effect of lead in occupationally exposed workers: a critical review.

Critical Reviews in Toxicology, 1990, 20(1): 237-255.

In their discussion of field testing of health effects of environmental and industrial toxins, Gullion and Eckerman make the following observations which can be applied to the current literature survey: "The general inattention to methodological consistency makes it difficult to integrate the research to date into a clear picture of what is known and not known about the effects of toxic substances on human behavior. In view of the variation of methods of subject selection, measurement, and statistical analysis, the completion of a series of studies of a particular toxic substance does not assure that there has been a concurrent accumulation of reliable knowledge about the effects of that substance. Apparent replications or failures to replicate a significant relationship must be evaluated carefully, since different studies may have measured different things in different populations." Therefore, the issue of psychological and neuropsychological effects of low-level lead exposure in adults remains to be resolved in the studies reviewed. The methodologies were so varied and the cultures in which the studies were conducted so diverse that it is impossible to generalize across findings. For example, studies were conducted in the U.S., Denmark, Sweden, Finland, and Australia. Although, in some instances, equivalent versions of neuropsychological and psychological tests were used, this was generally not the case. Nevertheless, a few general statements can be made. Studies that have been carried out in recent years are beginning to pay attention to more methodology and therefore do a much better of controlling for possible confounding variables. Also, their statistical methods are more sophisticated and reporting techniques are superior to the earlier investigations in this area. The issue of whether current blood lead levels or cumulative levels are preferable is still unresolved with regard to the relationship of neuropsychological impairment. In the area of psychosocial functioning, there appears to be at least some evidence to support the observation that increased irritability and fatigue may lead to the interpersonal problems noted in various studies. However, this observation may be related to other factors which have not been controlled for, such as the workers' attitudes toward their job, level of motivation, and overall level of mental health. With regard to neuropsychological functions, there is some suggestive preliminary evidence for subtle changes in the ability to process information quickly. (Abstract truncated at 100 words.)

Hammond PB; Dietrick KN.

Lead exposure in early life: health consequences.

Reviews of Environmental Contamination and Toxicology, 1990, 115: 91-124.

Until very recently it has been considered that of the many manifestations of lead toxicity, those involving the elaboration and function of hemoproteins occur at lower levels of lead exposure than any others. The critical target seems to be the enzyme heme synthetase, which is essential for the insertion of iron into the precursor, protoporphyrin IX. The major consequences of this effect, which have been evaluated in both adults and children, are reduction of circulating levels of hemoglobin and cytochrome P-150-dependent Phase I drug metabolism. Lead clearly inhibits normal hemoprotein function in both respects. The threshold level of lead exposure for these effects seems to be at a circulating lead of lead exposure for these effects seems to be at circulating lead concentration (PbB) of approximately 30 to 10 micrograms/dL. A growing body of evidence suggests, however, that the functional integrity of the central nervous system is compromised at maternal or cord PbB of somewhat less than approximately 10 micrograms/dL, a level of lead exposure not uncommon in the general population. Results of more recent cross-sectional and prospective studies indicate that postnatal lead exposure resulting in PbBs as low as 25 micrograms/dL, and probably lower, also are associated with deficits in intellectual attainment, achievement, and behavior. The long-term consequences of these effects remain to be fully evaluated. Little is known concerning basic mechanisms that are responsible for these effects. They may be manifestations of a more basic common effect of lead on cell proliferation and differentiation.

Ehle AL.

Lead neuropathy and electrophysiological studies in low level lead exposure: a critical review.

Neurotoxicology, 1986 Fall, 7(3): 203-216.

The literature on nerve conduction velocity (NCV) studies and electromyography in lead exposed populations was reviewed. All studies revealed some degree of defect in their experimental design. Disregarding these limitations, a consensus of the studies indicates that a mild slowing (7%) of motor and sensory NCV may be present in the median and posterior tibial nerves, but that ulnar and peroneal NCVs are not slowed in subjects with blood lead levels of less than 60 micrograms/dL. No clinical correlations to this mild slowing

were reported in studies where concurrent motor and sensory examinations were performed. A majority of the studies did not find a correlation between blood lead level and NCV at blood lead levels below 70 ug/dl or length of exposure and NCV. Most studies of electromyographic activity in lead exposed population found abnormalities only in patients with blood lead levels above 60-70 ug/dl or in patients with lead colic or other systemic systems of lead intoxication. This review does not find evidence that the slowing of NCV in low level lead exposure is clinically significant or evidence that would suggest that it is a subclinical manifestation of clinical lead neuropathy in man.

Ibele, LS; Pollock, CA.

Lead intoxication.

Med. Toxicol, 1986 Nov-Dec, 1(8): 387-410

Lead intoxication was recognized as early as 2000 BC and the widespread use of lead has been a cause of endemic chronic plumbian in several societies throughout history. In the twentieth century, lead intoxication is still a common problem. In children it is largely due to ingestion of pica and environmental exposure, whereas adult groups at greatest risk are the industrially exposed: thus, screening of these workers should be undertaken at regular intervals. The clinical features of lead intoxication are nonspecific and often go unrecognized. The early manifestations are largely neuropsychiatric, followed by more significant disturbances of the central and peripheral nervous systems, symptomatic gastrointestinal, musculoskeletal, hematological and endocrine abnormalities. The association of lead poisoning with renal disease is well documented and must be considered, particularly if there is associated hypertension and/or gout. Blood lead concentrations are an unreliable predictor of body lead stores as they are indicative only of recent exposure. Hematological parameters have been used to assess those at risk of toxicity. The recommended assessment for patients with suspected lead intoxication is a calcium disodium edetate chelation test, which is a sensitive marker for assessing body stores and subsequent intoxication. In children the dosage should be 50 mg/kg up to 1000 mg, and in adults 1000 mg administered intravenously or 2000 mg intramuscularly in divided doses 12 hours apart with subsequent 72 hour urinary lead estimations. Lead excretion levels greater than 350 micrograms/72 hours should be considered as suggestive of intoxication, particularly if supported by historical, clinical or biochemical evidence of lead exposure. Treatment of patients with positive chelation tests involves symptomatic treatment and a course of chelation therapy utilizing calcium disodium edetate in doses similar to those used for testing, and in the more severely intoxicated patient, the addition of dimercaprol in doses of 75 mg/m² every 4 hours to a total of 300 mg/m²/day. The safety of these treatment regimens is well documented.

EHLE, ALBERT & MCKEE, DAPHNE: Neuropsychological Effect of Lead In Occupationally Exposed Workers: A Critical Review. ILZRO Critical Review Series: Critical Reviews in Toxicology, Vol. 20, #4, pp 237-255. 1990 CRC Press.

ERNHART, CLAIRE B. ET AL: Lead Level and Iron Deficiency in the Preschool Years. Progress Report, ILZRO, June 1990.

ENSR HEALTH SCIENCES: The Reproductive Effects of Lead. ILZRO Feb. 1990.

FRIBERG, LARS: Handbook on the Toxicology of Metals, Volume I: General Aspects. 1986 Elsevier.

FRIBERG, LARS ET AL: Handbook on the Toxicology of Metals, Volume II: Specific Metals. 1986 Elsevier.

slowing were reported in studies where concurrent motor and sensory examinations were performed. A majority of the studies did not find a correlation between blood lead level and NCV at blood lead levels below 70 ug/dl or length of exposure and NCV. Most studies of electromyographic activity in lead exposed population found abnormalities only in patients with blood lead levels above 60-70 ug/dl or in patients with lead colic or other systemic symptoms of lead intoxication. This review does not find evidence that the slowing of NCV in low level lead exposure is clinically significant or evidence that would suggest that it is a subclinical manifestation of clinical lead neuropathy in man.

Note: a peripheral neuropathy
Lancet in 1985

G. CARDIOVASCULAR EFFECTS

All types of cardiotoxicity which occur in man with heart disease have been reproduced in experimental animals exposed acutely to high concentrations of lead or chronically exposed to lower levels.

Possible mechanisms of action are stated to be interference with central gamma-aminobutyric acid systems, alteration of adrenergic nerve development and lead-calcium interactions.

Electrocardiographic changes including T-wave changes, widened QRS-T angle and altered A-V conduction have been reported in children and adults suffering from acute lead intoxication. Such effects are reversible with treatment.

In addition, there are several reports suggesting that electrocardiographic abnormalities can be caused by chronic exposure to lead; however, at present day exposures it would not appear that these are directly associated with hypertension or other disorders of the cardiovascular system.

In the National Health and Nutritional Examination Survey II (NHANES II), blood lead concentrations were found to be higher in men and women who had hypertension than normal tensive persons of the same age, even though the blood concentration was within the numbers considered normal. In Cooper's 1985 study of the mortality of battery plant and production, workers during the years 1947-1980 there was a significant risk of excess deaths from hypertension, "other hypertensive diseases" and chronic nephritis found. It has been suggested that a major portion of chronic renal failure associated with essential hypertension may be due to a subtler excessive exposure to environmental lead. EDTA lead mobilization tests have produced a greater excretion of lead in persons with hypertensive disease than in patients with a comparable degree of renal failure due to other causes. This remains to be confirmed. A number of studies of the current levels of lead have failed to indicate a significant hypertensive effect in persons currently employed in the lead trades.

Recently as a result of the NHANES II Study, a question has been raised concerning a slight elevation in the systolic and diastolic pressure in middle-aged men with only background exposure to lead.

Dr. Gonick has proposed the following possible mechanism for this effect. Inhibition of Na-K-ATPase in vascular endothelium leading to an excess of cystolic ionized calcium within the smooth muscle of the vasculature. Increased pressor responsiveness to angiotension II and norepinephrine. Increased in renin activity and angiotension I.

V G

Pocock SJ; et al.

The relationship between blood lead, blood pressure, stroke, and heart attacks in middle-aged British men. Environmental Health Perspectives, 1988 Jun, 78: 23-30.

The relationship between blood lead concentration and blood pressure is examined in a survey of 7371 men aged 40 to 59 from 24 British towns. After allowance for relevant confounding variables, including town of residence and alcohol consumption, there exists a very weak but statistically significant positive association between blood lead and both systolic and diastolic blood pressure. These cross-sectional data indicate that an estimated mean increase of 1.45 mm Hg in systolic blood pressure occurs for every doubling of blood lead concentration with a 95% confidence interval of 0.47 to 2.13 mm Hg. After 6 years of follow-up, 316 of these men had major ischemic heart disease, and 66 had a stroke. After allowance for the confounding effects of cigarette smoking and town of residence there is no evidence that blood lead is a risk factor for these cardiovascular events. However, as the blood lead-blood pressure association is so weak, it is unlikely that any consequent association between lead and cardiovascular diseases could be demonstrated from prospective epidemiological studies. An overview of data from this and other large epidemiological surveys provides reasonably consistent evidence on lead and blood pressure. While NHANES II data on 2251 U.S. men indicate a slightly stronger association between blood lead and systolic blood pressure, data from two Welsh studies on over 2000 men did not show a statistically significant association. However, the overlapping confidence limits for all these studies suggest that there may be a weak positive statistical association whereby systolic blood pressure is increased by about 1mm Hg for every doubling of blood lead concentration. (Abstract truncated at 250 words)

Rabinowitz M; et al.

Pregnancy hypertension, blood pressure during labor, and blood lead levels.

Hypertension, 1987 Oct, 10(1): 447-451.

Pregnancy hypertension, blood pressure during labor, and the umbilical cord blood lead concentration were assessed in 3851 women for whom additional demographic, medical, and personal information was available. Lead levels correlated with both systolic (Pearson $r = 0.081$, $p = 0.0001$) and diastolic ($r = 0.051$, $p = 0.002$) blood pressures during labor. The incidence of pregnancy hypertension increased with lead level. Multivariate models of pregnancy hypertension and

systolic blood pressure as a function of maternal age, parity, hematocrit, ponderal index, race, and diabetes were improved by including lead as a predictor variable. At these observed levels of exposure (mean blood lead, 6.9 ± 3.3 [SD] micrograms/dl), lead appears to have a small but demonstrable association with pregnancy hypertension and blood pressure at the time of delivery, but not with preeclampsia.

H. LIVER

At the present time it does not appear that there are even significant sub-clinical effects of lead on the liver. One report did indicate an elevation of SGOT values in smelter workers.

Alcoholic intake was not reported. There are data which suggests interference with hydroxylation of 1-OH Vitamin D to the 1,25 OH form.

I. RESPIRATORY

Inhalation of fumes of lead or its oxide are not irritating to the respiratory tract. Aerosols of the salts of lead and strong acids may be.

J. ENDOCRINE ORGANS

Lead has been implicated as possibly causing impairment of thyroid and adrenal function in children. There is also an indirect effect on the parathyroid gland.

Persons who were judged to have lead intoxication on the basis of their urinary excretion of lead following a challenge with EDTA, had decreased uptake of iodine with a mean value of only 10 percent. An additional 12 percent of the group did not respond normally to stimulation of the thyroid with STH. Other measurements of the thyroid function were normal.

Other possible effects include decreased pituitary gland reserve and decreased adrenal gland activity to challenge by ACTH. Aldosterone secretion rate is depressed during salt restriction in lead poisoning. Parathyroid hormone mobilizes lead from the skeleton, increases its concentration in the blood and its urinary excretion.

K. SKIN

The salts of lead with strong acids (lead chloride and lead nitrate) are irritating to the skin. Lead metal and its oxides are not. Lead does not penetrate the skin but may enter the body if open wounds have contact.

L. MUSCULOSKELETAL

Lead may have an inhibiting effect on calciferol synthesis and calcium deposition in bones. Bone density is increased in leaded children at the epiphysitional line but not in adults. There is, however, a slight generalized increased bone density with increased lead uptake. Bones do not become

V I

Maaledi MR; et al.

- ✱ Pulmonary complications in lead miners.
Chest, 1989 Jul, 96(1): 18-21.

We carried out a study to assess the prevalence of respiratory disease in lead miners and to investigate the roles of silica and lead. We used a questionnaire for symptoms and examinations for signs of respiratory disease, chest roentgenograms, and spirometric study in 45 lead miners. Six underwent bronchoscopy and transbronchial lung biopsy (TBB) and five lung lead analysis. Lung lead levels from five patients with no occupational lead exposure were obtained for comparison. Results showed restriction in five of 45 and reticulonodular opacities in 16 of 45 workers. Squamous metaplasia and other histopathologic changes were observed, although silicotic nodules were absent by TBB. Lung lead levels above those of control subjects were observed in four of five lead miners. These findings show that lead miners are at risk for lung disease. Although silica is a likely cause, elevated lung lead content found in these miners merits further investigation.

NONE = NO EFFECT FROM Pb.

SILICA, OTHER MINED
DUSTS MAY BE IMP T.

V J

Govon S; et al.

- ✱ Plasma prolactin concentrations in lead exposed workers.
Journal of Environmental Pathology, Toxicology and Oncology, 1987 Mar-Apr, 7(4): 13-16.

Plasma Prolactin (Pr1), Zinc protoporphyrin (ZPP), and blood lead concentrations (PbB) were measured in 76 exposed male workers. All of them were employed in small (not more than 30 persons) pewter factories and were randomly selected from those regularly controlled by the National Health Service, Occupational Health Unit of Brescia (USSL 41). Although all plasma Pr1 values were within the normal range, the mean value of the subgroup having ZPP and PbB higher than 40 micrograms/dl was significantly higher (+47%) than that observed in the group of workers having ZPP and PbB less than 40 micrograms/dl. The data indicate the possibility of a lead-induced Pr1 secretion dysfunction, probably mediated by a decrease in dopaminergic inhibitory control.

Bielecke W; et al.

[Thyroxine (T4) levels in workers exposed to lead].

Language: Polish

Medycyne Pracy, 1987, 38(1): 40-44.

Thirty men occupationally exposed to lead have been examined.

The selection of subjects was based on increased lead poisoning indices as well as on the data proving there had been no thyroid disease incidence noted prior to the lead poisoning. Each of the subjects underwent determination of T4 concentration simultaneously with the measurement of three basic indicators of lead poisoning: ALA in urine and ZPP and Pb in blood. Three T4 concentration ranges have been obtained therefore all the cases have been divided into three groups: I increased T4 concentration; II normal T4 concentration; III decreased T4 concentration. In each group T4 concentrations have been compared with the poisoning indicators. The highest poisoning indicators have been found in group II exhibiting normal T4 concentrations (43.33% of cases). It differed significantly from group III (50.0% of cases) exhibiting decreased T4 concentrations. The determination values in Group I (increased T4 concentrations) have been excluded from statistical calculations, as there were too few cases (6.67%). The discrepancy of T4 results, their pathological picture at lower values of poisoning indices evidence that the establishment of Pb effects upon thyroid function would call for the determination of a number of additional factors possibly affecting the mechanism handling this phenomenon.

Gustafson A; et al.

Occupational lead exposure and pituitary function.

International Archives of Occupational and Environmental Health, 1989, 61(4): 277-281.

Twenty-five moderately exposed lead workers (mean blood-lead level 1.8 $\mu\text{mol/l}$) had lower plasma levels of follicle stimulating hormone than 25 individually matched controls without occupational lead exposure (blood lead level 0.2 $\mu\text{mol/l}$). In addition, the ten most heavily exposed individuals had higher levels of thyroid stimulating hormone, and the 14 workers under the age of 40 had decreased plasma levels of lutenizing hormone and serum levels of cortisol, as compared to the controls. All values were within "normal" reference limits. There was no significant change of the plasma testosterone level. These data indicate a complex effect on the endocrine system by moderate lead exposure, possibly mediated by changes at the hypothalamic-pituitary level. Besides the effect on hormone levels, there was also a decrease in plasma selenium level for the lead exposed workers.

Apostoli P; et al.

✕ [Possible effects of lead on various hormonal metabolic pathways].

Language: Italian

Giornale Italiano di Medicina del Lavoro, 1988 Jan, 10

(1): 19-22

After reviewing the principal studies on the interferences of lead on the endocrine system, this paper reports the results of a survey carried out on 30 subjects in which the effects of lead on serum FSH, LH and testosterone and on urinary steroid hormones excretion were examined. Statistically significant differences were not demonstrated between lead exposed subjects and control group for serum LH and testosterone (total and free) and for urinary steroids. A significant increase remains between the "normal limits" of the laboratory which performed the determinations. The results are discussed in the light of the more recent knowledge about the endocrine effects of xenobiotics in general and heavy metals in particular and some interpretations to justify the detected FSH increase are proposed.

?

Siegel M; et al.

The effect of lead on thyroid function.

Environmental Research, 1988 Aug, 49(2): 190-196.

Exposure to inorganic lead has been associated with impaired uptake of iodine by the thyroid as well as depressed estimated free thyroxine levels in occupationally exposed adults. Consideration of the serious consequences of impaired thyroid function in young children prompted investigation of the effects of lead on thyroid function in children. Blood lead determinations and thyroid functions tests were performed on 68 children examined at a hospital outpatient pediatric clinic. Serum thyroxine (T4) and free thyroxine (FT4) levels were within the normal range for all patients. No statistically significant relationship was found between lead levels and T4 or FT4 levels. We conclude that lead is unlikely to have a clinically significant effect on thyroid function in children exposed in inner cities at prevailing levels.

brittle as in fluoride poisoning Muscle cramps, weakness and myalgias occurs in systemic poisoning. In severe cases, muscle weakness progresses to paralysis and atrophy.

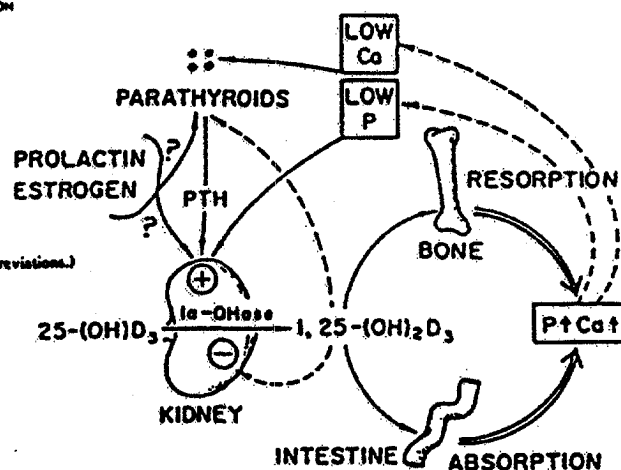
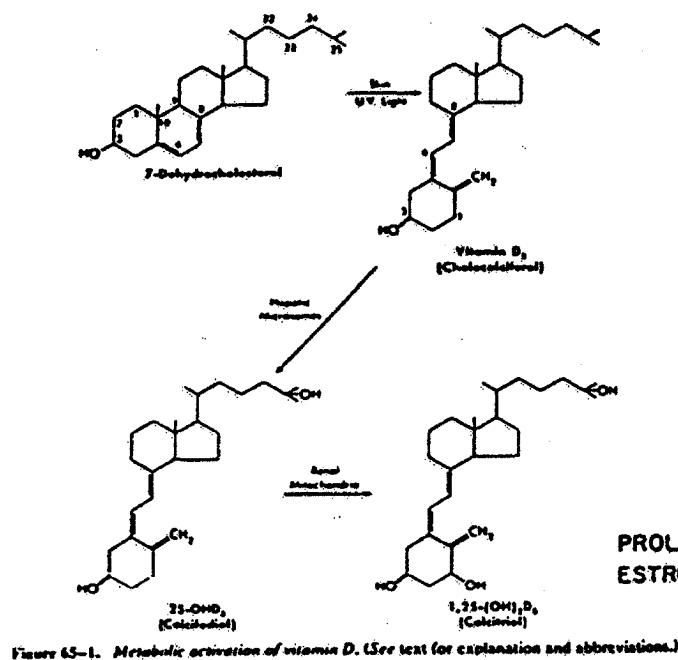


Figure 65-2. Model for regulation of the biosynthesis of $1,25-(OH)_2D_3$.

Solid arrows indicate a positive effect; dashed arrows refer to negative feedback (see text for explanation). (Modified from Haussler and McCain, 1977. Courtesy of the *New England Journal of Medicine*.)

M. IMMUNE SYSTEM

There are no definite studies which link the immune dysregulation with increased body burdens of lead.

IV L

Christofferson J.O. et al.

- * Decrease of skeletal lead levels in man after end of occupational exposure.

Archives of Environmental Health, 1988 Sep-Oct, 11(5):312-8.

Lead levels in finger bone were monitored using an in vivo x-ray fluorescence technique in retired lead workers. Eight subjects followed for 2-5 years directly after end of exposure all displayed a decrease. Their average half-time was 7 (range 3-15) years. In a second group of six persons, followed from year 7 to year 13 after finishing lead work, a decrease was seen in all but one. The average half-time for this group was 8 (range 2-infinity) years. The mean value for both groups was 7 years. The results show that there is a decrease of lead in bone after the end of exposure and that it is considerably faster than estimated earlier from various data on lead metabolism.

Silbergeld, E.K. et al.

- * Lead and osteoporosis: mobilization of lead from bone in postmenopausal women.

Environmental Research 1988, Oct, 47(1):79-94.

Although it has been known that humans accumulate lead in bone, mineralized tissue has been considered primarily as a sequestering compartment and not as a site of toxic action for lead. However, experimental data indicate that bone lead can be released during conditions of demineralization, such as pregnancy and lactation. We have examined lead status in women, before and after menopause, using the NHANES II dataset compiled between 1975 and 1980. In 1981 black and white women, there was a highly significant increase in both whole blood and calculated plasma lead concentration after menopause. The results indicate that bone lead is not an inert storage site for absorbed lead. Moreover, lead may interact with other factors in the course of postmenopausal osteoporosis, to aggravate the course of the disease, since lead is known to inhibit activation of vitamin D, uptake of dietary calcium and several regulatory aspects of bone cell function. The consequences of this mobilization may also be of importance in assessing the risks of maternal lead exposure to fetal and infant health.

Schutz, A. et al.

Chelatable lead versus lead in human trabecular and compact bone.

Sci Total Environ. 1987, Mar, 51:201-209.

In active and retired lead workers there was a close correlation between urinary excretion of lead during five hours after intake of a single oral dose of 0.5 grams penicillamine and the excretion during 24 hours. In chelation tests, it is thus sufficient to collect urine for only a few hours. There was a close correlation between the amount of chelatable lead and the

blood lead level, as well as the lead level in biopsies of trabecular bone from vertebrae, but there was no association with lead in compact bone, as measured in finger-bone by in vivo x-ray fluorescence. The chelatable lead probably mainly reflects the soft tissue lead pool and a fraction of the trabecular bone lead pool, which has a relatively rapid turnover. It is not a valid indicator of the pool of lead which has slowly accumulated in the compact bone and it is thus not useful as a time-integrated index of the exposure over a long period of time.

Wittmers, L.E. Jr. et al.
Lead in Bone. IV Distribution of lead in the human skeleton.
Archives of Environmental Health, 1988 Nov-Dec, 43(6):381-391.

Flameless atomic absorption spectroscopy was used to measure lead concentrations in samples from five selected human skeletal sites (tibia, skull, ilium and vertebra) obtained from 134 hospital autopsies. Lead was distributed unequally among the different bones in distinct patterns that were age- and, to some extent sex-dependent. To estimate lead concentration of the entire skeleton, all skeletal bones were divided into five groups based on their approximate compact/trabecular bone ratios, considering each of our five sampled sites to be the prototype for each such group. Regression analysis of the ten possible bone site pair values at different ages yielded age-related constants. These constants were incorporated into an equation we developed that can be used both to estimate mean skeletal lead concentration (Pb) of the entire body skeleton and also to predict the lead concentration at any of the other four bone sites if any one of the five is measured. Applications of these data to in vivo bone lead measurements are detailed with respect to selection of the site to be measured, estimation of total skeletal lead burden, anticipated variations of error and dependence of these factors on age and sex of the sampled population.

Schutz, A. et al.
Kinetics of lead in blood after the end of occupational exposure.
Scandinavian Journal of Work, Environment and Health, 1987, June, 13(3):221-31.

The sum of two exponential functions was fitted to the decay of blood lead (PbB) level after the end of exposure. For two subjects who had not formerly been occupationally exposed to lead but who had been exposed to a single short heavy dose, the fast compartment (probably soft tissues) had a biological half-time of 27 and 44 d respectively. For twenty lead workers after the end of occupational exposure, the corresponding median was 29 (range 7-53). For 21 ex-lead workers, the median biological half-time of the slow compartment was 5.5 years

(range 2.3-27). There was significant interindividual variation in both the fast and the slow half-time. This finding probably means a considerable variation in risk at a certain exposure level. In the lead workers, the PbB fraction corresponding to the slow compartment had a median as high as 1.8 $\mu\text{mol/L}$ (range 0.7-2.7), which constituted more than half of the total PbB. This fraction was associated with exposure history, and with the lead level in the skeleton, the latter determined in vivo by an x-ray fluorescence method. The data thus indicate a rather rapid turnover of the skeletal lead pool, a phenomenon which may affect the PbB level considerably.

V. MUTAGENESIS AND CANCER

A. MUTAGENESIS

Mutagenesis is the term applied to the phenomenon of the changes which occur on abnormal replication of a cell. Most mutagenic changes are detrimental to the host. They can produce cancer (somatic changes) and abnormal products of conception (germinal tissue).

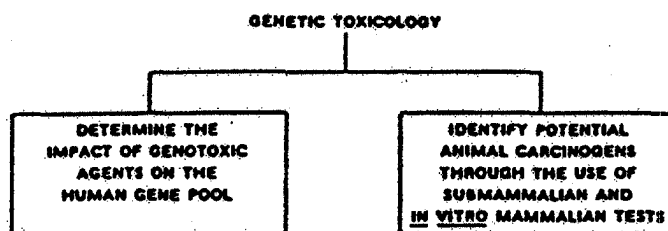


Figure 3.1. The two roles of genetic toxicology which have been forcing factors in its development as a discipline.

immediately if it is dominant, or it may not be expressed for several generations if it is recessive. Human epidemiological studies are of limited value in developing a case for restriction of mutagens because, in most cases, the cause-and-effect portions of the relationship are separated by a considerable length of time. Concern over genotoxicity must be developed through an awareness of the serious consequences likely to occur 100 years or more from today if human exposure to significant levels of mutagenic agents is not prevented.

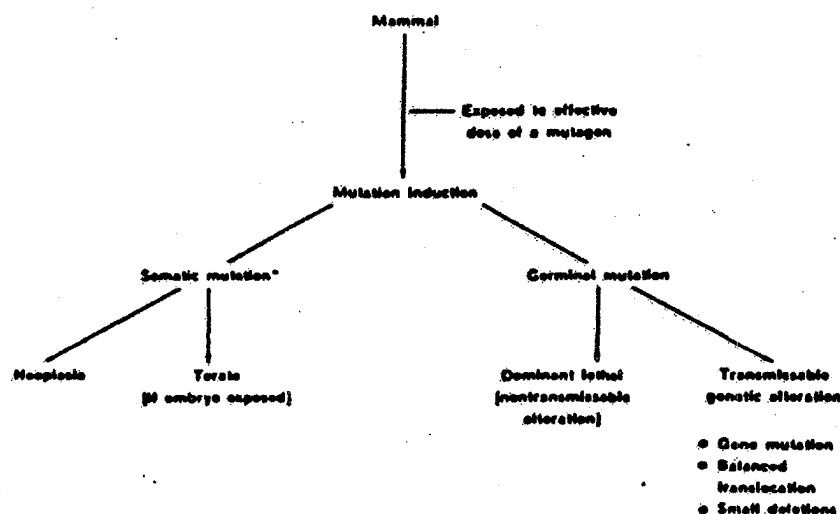


FIGURE 3.2. Possible mutagenic effects in mammals. The location of the mutagenic event is important in determining whether its effect will have an impact on the exposed individual or individuals in subsequent generations. Somatic cell alterations can be detrimental to exposed individuals, whereas the alterations induced in germ cells will affect subsequent generations. * Also implicated in certain types of heart disease. From Brusick, D. J.: Alterations of germ cells leading to mutagenesis and their detection. *Environ. Health Perspectives* 24:105-112, 1979.

IV M

Kimber, I. et al.

✕ Influence of chronic low-level exposure to lead on plasma immunoglobulin concentration and cellular immune function in man.

International Archives of Occupational and Environmental Health, 1986, 57(2):117-25.

No 4's
The immunological status of individuals exposed to low levels of inorganic lead has been examined and compared with that of non-exposed, age and sex-matched controls. At the time of testing, the exposed population had a mean ($\pm$ SD) blood lead concentration $38.4 \pm 5.5 \mu\text{g} \times 100\text{ml-L}$ ($n = 39$) compared with a mean value of $11.8 \pm 2.2 \mu\text{g} \times 100 \text{ ml-L}$ ($n = 21$) for the control group. No differences in the serum concentrations of IgG, IgA and IgM between the populations were observed and there existed no correlation between blood lead concentration and serum immunoglobulin levels. In addition, assessment was made of the capacity of peripheral blood mononuclear cells to respond to the mitogen phytohemagglutinin (PHA), a correlate of T cell function, and to spontaneously lyse cells of the erythroleukemic cell line K5S2, a measure of NK cell function. In neither case was there a difference between exposed and control populations and no correlation between reactivity and blood lead concentration. Although previous studies in rodents have indicated that exposure to inorganic lead resulting in similar blood lead concentrations may compromise immune competence, our data suggest that no similar effect occurs in man.

Cohen, N. et al.

Increased concanavalin A-induced suppressor cell activity in humans with occupational lead exposure.

Environmental Research, 1989 Feb, 49(1):1-5.

E-rosette-forming cells (E-RFC), mitogen-induced blast transformation, OKT4+, OKT9+ cells and their ratio were found to be normal in 10 subjects normally exposed to lead with blood levels of 40-51 $\mu\text{g}\%$. However, concanavalin A (Con A)-induced suppressor cell activity (SCA) in these subjects was significantly greater than in normal matched controls. The clinical relevance of this observation is not clear, but it may have some bearing on the various immunologic defects described in lead exposure.

Governe, M. et al.

Impairment of chemotaxis of polymorphonuclear leukocytes from lead acid battery workers.

Sci Total Environ, 1988, Jun 1, 71(3):543-5.

Since lead impairs in vitro the functions of macrophagic cells, we have studied the chemotactic activity of polymorphonuclear leukocytes (PMN's) obtained from lead acid battery workers who were removed from exposure one month before because they had an

abnormal lead absorption. Controls were 19 matched subjects without any history of occupational lead exposure. Both lead acid battery workers and controls had no alterations of the blood hematological and metabolic parameters. Chemotaxis was carried on in Boyden chambers using zymosan-activated serum as chemotactic stimulus. The chemotactic indexes are 55.4 ± 8.7 in acid battery workers and $75.6 \pm$ in controls. The difference, which is statistically significant, shows that lead workers have an impairment of PMN's chemotactic activity.

V A

Zelikoff, J.T.

Genetic toxicology of lead compounds.

Carcinogenesis, 1988, Oct, 9(10):1727-32.

We have investigated the activity of insoluble and soluble lead compounds in inducing mutagenesis, cell transformation and sister chromatid exchange in mammalian cells. Insoluble lead sulfide, readily phagocytized, was more than four times as toxic to V79 cells on a microM basis, than two moderately soluble lead compounds although the exposure time for the soluble salts was five times longer. These findings demonstrate the importance of different cellular mechanism(s) of metal uptake and bioavailability. Both insoluble lead sulfide and more soluble lead nitrate were mutagenic at the HPRT locus in V79 cells. Although less mutagenic at the higher concentrations, lead nitrate at a concentration of 500 microM enhanced the mutation frequency greater than five-fold above background following a five day exposure. Although the mechanism(s) by which lead induces mutations is not known, failure of both compounds to induce SCE and DNA single-strand breaks, detectable by alkaline elution, suggests that lead-induced mutations may not be a result of direct damage to DNA but may occur via indirect mechanisms including disturbances in enzyme functions important in DNA synthesis and/or repair, or in DNA-helical structure. Lead acetate also transformed SHE cells in a dose-response fashion following a 48 hour exposure. Our results indicate that lead compounds may be genotoxic by an indirect mechanism, and lead support to the view that lead is a carcinogen.

Apostoli, P. et al.

* Urinary mutagenicity tests in lead-exposed workers.

Mutation Research, 1989, Mar, 222(3):245-51.

Urinary mutagenic activity detected by the bacterial fluctuation assay, using *Salmonella typhimurium* TA98 and *Escherichia coli* WP2 uvrA with and without metabolic activation (S9 mix), was studied in a group of 21 workers exposed to inorganic lead and a control group of 22 non-occupationally exposed subjects. Occupational exposure to inorganic lead had no effect on urinary mutagenicity in the strains considered, with or without metabolic activation. In smokers (exposed and non-exposed), urinary mutagenicity activity appeared to increase compared to non-smokers (exposed and non-exposed), only with *Salmonella typhimurium* TA98 in the presence of S9 mix.

Evaluation of the rate and type of mutagenesis can be made by examination of the chromosomes in dividing tissue. e.g., white cells, sperm, mucous membrane cells, lung, the buccal cavity and gastrointestinal tract.

Abnormalities of cells can be seen in the anatomic arrangement and number of chromosomes (Denver Classification) and the number of sister chromatid exchanges (SCE).

There is no known evidence of chromosomal effects. Lead compounds have not given rise to mutagenic effects in bacterial testing systems. However, they have been positive in other experimental systems. As regards human exposure, IARC referred to seven studies with negative and nine with positive results. Local environmental exposures and mixed occupational exposures of groups give rise to difficulty in the interpretation of positive results.

I have concluded that there are no convincing data which indicate that mutagenic effects are likely to occur in man as a result of elevated lead body burden.

Studies of genotoxicity of lead and its compounds have been carried out on microbial systems, fruit flies, algae, plants, mammalian cells in vitro, mammals in vivo and man in vivo. The results are both positive and negative. The only positive effects in in vivo study in man were reported by Forte and Secchai in 1972. Five other investigators found no effects.

B. CANCER

1. Animal Experiments

Cancer of the kidney is produced by administration of soluble lead compound to mice and rats, but to no other species.

2. Epidemiologic Studies of Man

Cooper and coworkers have published a series of papers relating to the mortality pattern among smelter workers and battery plant workers. Their last publication (1984) which included a group from the period 1947-1980 found no elevated standardized mortality ratios for malignant neoplasms of either battery or smelter workers. There had been an excess of stomach cancers which became negative on a case-control study. In 1980 IARC concluded that it would be reasonable to regard lead acetate, lead sub-acetate and lead phosphate as representing a carcinogenic risk to humans. As the kidney is the only organ clearly implicated in experimental cancer with lead compound studies, assessing lead exposures in cases of renal cancer would be indicated. It should be considered that while these soluble lead compounds are

Lead and Cancer Research

ILZRO has developed a lead and cancer research program that will retrospectively look at work that has been done which suggested a link between lead and cancer, and to initiate projects that will develop new information to support or refute the association between lead and cancer. The program has six basic elements which include the following:

- Critically review the Azar Lead Acetate Cancer Bioassay
- Evaluate the Molecular Mechanisms Responsible for the Induction of Nephrotoxicity and Kidney Carcinogenesis in the Rat
- Determine if Epidemiological Evidence exists linking Lead and Cancer
- Perform a Lead Oxide Inhalation Study
- Study the Cytotoxic Characteristics of Different Lead Compounds
- Prepare a Cancer White Paper

With the exception of a White Paper Preparation and the Inhalation Study, EPA is a participant and financial supporter of these projects, while IARC will likely participate in any epidemiological work.

carcinogenic to experimental animals, human beings are exposed primarily through metallic lead and lead oxide.

Observed and expected deaths in 1947-1960 in a cohort of 2 300 workers employed in lead production facilities for at least one year between 1 January 1946 and 31 December 1970 - Comparison with US white male rates.*

Cause of death ^b	Deaths		Standardized mortality ratio	95 % confidence limits
	Observed	Expected		
All malignant neoplasms (140-205)	120	105.9	113	94-136
Digestive organs and peritoneum (150-159)	36	30.5	118	83-164
Stomach (151)	9	8.2	148	67-278
Large intestine (153)	6	9.5	63	23-138
Liver (155)	4	2.2	184	50-471
Respiratory system (160-164)	43	34.9	123	89-166
Larynx (161)	2	1.6	122	15-441
Bronchus, trachea, lung (162-163)	41	32.9	125	89-169
Kidney (180)	2	2.7	75	9-270
Brain and other central nervous system (183)	3	3.3	90	19-264
Lymphoproliferative system (200-205)	10	10.7	94	45-

A study of the cause of death of all male workers who were employed at the Ronnskar Works from 1950 to 1981 was made. Overall, in the smelter which produced copper, lead and arsenic, there was a considerable excess of deaths from malignant neoplasms of the lung and stomach. However, there were no significant differences found for any malignancy between high lead and low lead exposure of these smelter workers exposed previously to lead. This data is interpreted as strengthening the evidence that lead is not a carcinogen in man.

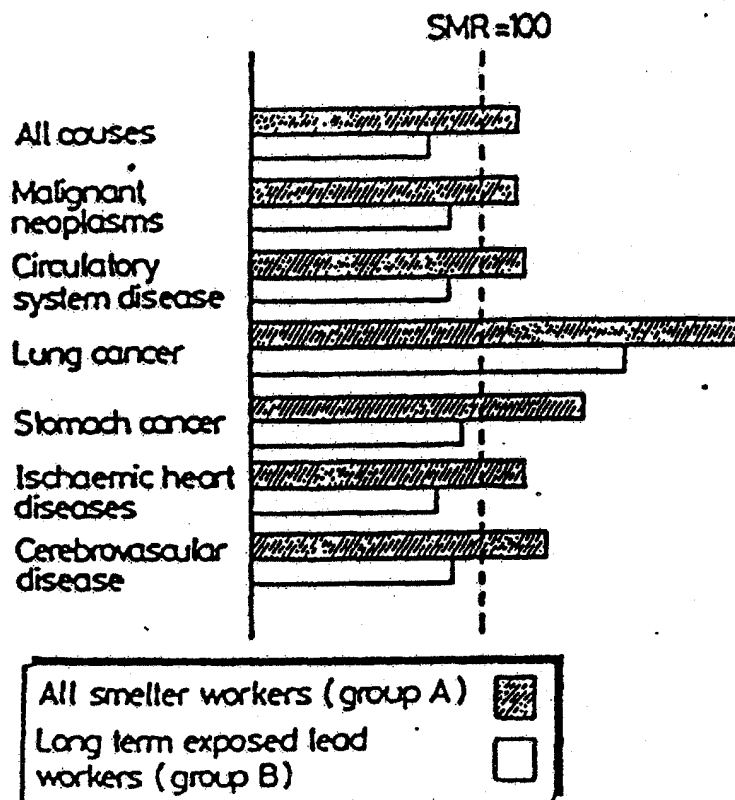


Fig 3 Standardised mortality pattern 1950-81 for all smelter workers (group A) and lead smelter workers (group B) by reference to the Swedish male population.

Human Cancer Risk Associated with Lifetime
Daily Oral Intake of Lead

Daily Dose, ug	MLE ^a	Upper 95% C.L. ^b
100	3.6×10^{-9}	1.1×10^{-5}
10	3.6×10^{-11}	1.1×10^{-6}

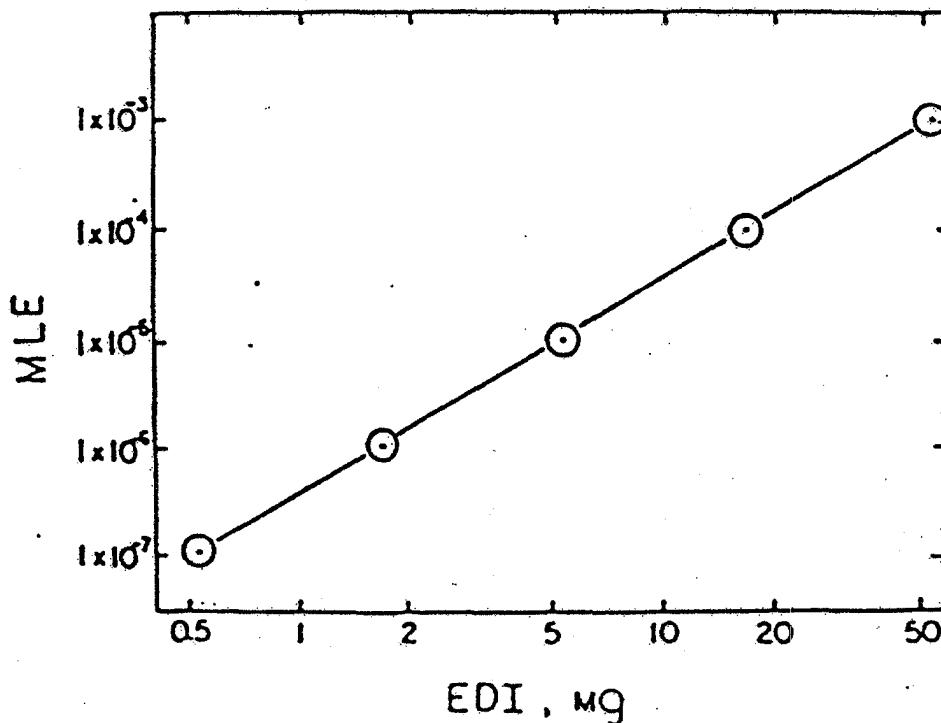
^aMLE-maximum likelihood estimate e.g. 3.6 chances in 1 billion (10^{-9}).

^bupper 95% confidence limit for the estimate

Maximum Likelihood Estimates (MLE) for Cancer Risk
and Estimated Daily Oral Lead Intake (EDI)

MLE	EDI, mg
1×10^{-3}	53
1×10^{-4}	16.8
1×10^{-5}	5.3
1×10^{-6}	1.7
1×10^{-7}	0.53

RISK ESTIMATE FOR CANCER IN MAN AS DERIVED FROM
THE ANIMAL STUDIES OF AZAR *et al.* (1973)^a



^aMLE = Maximum likelihood estimate (see text)
EDI = Estimated daily oral intake of lead

V B2

Buckley, J.D. et al.
Occupational exposures of parents of children with
acute nonlymphocytic leukemia: a report from the
Childrens Cancer Group.
Cancer Research, 1989 Jul 15, 49(14):4030-7.

The Childrens Cancer Study Group conducted a case-control study of occupational exposures of parents of 204 children (under 18 years of age), with acute nonlymphoblastic leukemia. The most consistent finding was an association of acute, nonlymphoblastic leukemia risk with pesticide exposure. Controls matched by date of birth and race were obtained through random digit dialing. Odds ratio (OR) for paternal pesticide exposure in jobs held for longer than 1000 days was 2.7% (95% confidence interval, 1.0 to 7.0; trend, $P = 0.05$), and seven case mothers and no control mothers had prolonged exposure (trend, $P = 0.008$). Risk estimates for parental pesticide exposure were substantially increased for children under age 6 at diagnosis (OR for prolonged exposure to either parent = 11.4; trend, $P = 0.003$) and for those with myelomonocytic and monocytic subtypes (OR, 13.6; trend, $P = 0.007$). Moreover, there were significantly elevated risks for direct exposure of the child to pesticides in the household (OR for exposure most days = 3.5; trend, $P = 0.04$) and for maternal exposure to household pesticides at the time of pregnancy (eight case mothers versus no controls for exposure most days; trend, $P = 0.05$). Paternal exposures to solvents (OR, 2.1; $P = 0.003$) and petroleum products (OR, 2.4; $P = 0.002$) were reported more commonly for cases than controls. Other occupational exposures reported significantly more often by case parents were paternal exposure to plastics or lead and maternal exposure to paints and pigments, metal dusts and sawdust. These data provide further evidence for a role of occupational risk factors in the etiology of childhood cancer.

Wickland, K.G. et al.
Respiratory cancer among orchardists in Washington
State, 1968 to 1980.
Journal of Occupational Medicine, 1988, Jul,
30(7):561-4.

A case control investigation was conducted to evaluate the hypothesis that past exposure to the pesticide lead arsenate led to an excess mortality from respiratory cancer. Cases included all white male orchardists who died in Washington State between 1968 and 1980 from respiratory cancer. Orchardists who died of other causes during this period served as controls. Occupational and smoking data for 155 case subjects and 155 control subjects were obtained via telephone interview with next-of-kin/informants. Neither presence, intensity, nor duration of lead arsenate exposure differed between case and control subjects. Although cigarette smoking was unusually common among cases of respiratory cancer, smoking habits of the

orchardists and a sample of non orchardists who had died of other causes were quite similar. The cause of the excess mortality from respiratory cancer among Washington State orchardists remains unknown.

Fanning, D.

A mortality study of lead workers, 1926-1985.

Archives of Environmental Health, 1988, May-Jun, 43(3):247-51.

SWEDEN

In a case-control study of 867 deaths between 1926 and 1985 of men who had relatively high occupational lead exposure, compared with 1,206 who died during the same period, and whose lead exposure had been low or absent, there was a statistically significant excess of deaths from cerebrovascular disease between 1946 and 1965. There were also signs of a decreasing secular trend in the odds ratios for deaths from this cause between 1926 and 1985, with no difference between the two groups over the past 20 years. There was no statistically significant excess in the number of deaths from malignant neoplasms, either in general, or for specific sites. Previous evidence of an increased risk of death from cerebrovascular disease is therefore confirmed, but it would seem that with the introduction of stricter standards of lead control, that this has now disappeared, as has any marginal risk of death from malignant disease.

Pb

ALONE

lung cancer
slight

Gerhardsson, L. et al.

Mortality and lead exposure: a retrospective cohort study of Swedish smelter workers.

British Journal of Industrial Medicine, 1986, Oct, 43(10):707-12.

The study is based on the work histories and mortality data for 3832 male workers first employed before 1957 at a copper smelter in northern Sweden and followed up from 1950 to 1981. From the 3832 workers, a lead cohort consisting of 437 workers employed for at least three years at sites with considerable lead exposure during 1950-74, was selected. These workers had regular blood lead measurements performed since 1950. Based on the cumulative blood lead dose 1950-74 and peak blood lead values, the cohort was subdivided into high mean, low mean, high peak and low peak groups. Standardized mortality ratios (SMR's) were calculated for the six groups using general and local reference populations. The original cohort of 3832 workers showed considerable excess of deaths for total mortality, malignant neoplasms (especially lung and stomach cancer), ischemic heart diseases and cerebrovascular diseases when compared with the general population. In the lead cohort where the workers had been subjected to a considerable lead exposure, only the raise SMR for lung cancer was sustained (SMR = 162; not significant). No significant differences were found between high lead and low lead exposed smelter workers.

VI. LEAD INTOXICATION

Toxicity of Lead. The toxicity of lead depends on the rate, route and duration of exposure, the age of the person and the total amount in soft tissues.

<u>Intake</u>	<u>Effects</u>
1 mg/day	Slight positive balance
10 mg/day	Marked positive balance
100 mg. single dose	Some symptoms
1000 mg. single dose	Marked symptoms
10,000 mg. single dose	Lethality

A. DEGREE

1. Subclinical. This term is applied to those cases where there are measurable changes in the lead body burden beyond that which is generally accepted as normal and some measurable effect are observed by laboratory investigations which are compatible with the known effects of lead. For example, there would occur a rise in the FEP, increased excretion of coproporphyrin, prolongation of nerve conduction time. An increase in the body burden of lead does not in itself constitute subclinical intoxication.

- a) Mild
- b) Moderate
- c) Severe

The signs and symptoms generally associated with these three grades of intoxication are summarized below.

SIGNS OF LEAD POISONING

<u>MILD</u>	<u>MODERATE</u>	<u>SEVERE</u>
Anemia, Slight	Anemia, Moderate	Anemia, Marked
Decreased Hand Grip	Decreased Muscle Mass	Ankle Palsy
Decreased Muscle Tone	Eyelid Tremor	Convulsions
Discomfort on Abdominal Palpation	Fasciculation	Elevated Blood Pressure
Pallor	Flexor Weakness	Kidney Tenderness
Renal function, Borderline Changes	Renal Dysfunction, Slight	Renal Insufficiency
Restlessness	Hyporeflexia	Marked Weight Loss
	Lead Line	Obtundation
	Tongue Tremor	Wasting
		Wrist Palsy

VI A1

He, F.S. et al.
 An electroneurographic assessment of subclinical lead toxicity.
 International Archives of Occupational and Environmental Health, 1988, 61(1-2):141-5.

While heavy exposure to inorganic lead is capable of inducing symptomatic neuropathy in man, the subclinical neuropathy due to low levels of occupational lead exposure remains to be proved. The reported results of electroneurographic studies on lead workers, however, have been controversial. In this study, 40 lead smelter workers and 50 non-exposed referents were investigated. The air concentrations of lead at worksites were 0.25 to 42.5mg/m³. The geometric means of PbB, PbU and delta-ALAU in the lead exposed group were 40.03ug/dl, 71ug/l and 4.58mg/l respectively, which were significantly higher (P less than 0.001) than those (7.01ug/dl, 5.0ug/l and 1.81mg/l respectively) in the reference group. There were no clinical symptoms or signs of nerve damage in either group. Alcoholism and diabetes were excluded in both groups. Nerve conduction velocity was measured by a DISA 1500 electromyograph in both groups. Eleven electroneurographic parameters, including motor nerve conduction velocity (MCV) and distal latency (DML) of median, ulnar and peroneal nerves as well as sensory nerve conduction velocity (SCV) and distal latency (DSL) of median, ulnar and sural nerves, showed statistically significant differences between the two groups. However, the results of electroneurographic measurements of each individual in the lead-exposed group were all within the normal range. There was no correlation between the blood lead levels and the neurophysiological measurements except for the median MCV. No correlation was seen between the MCV and the exposure duration.

VI B3

Lolin, Y. & Gorman, P.
 Delta-aminolaevulinic acid dehydratase as an index of the presence and severity of lead poisoning in acute and chronic lead exposure.
 Annals of Clinical Biochemistry, 1986, Sep, 23 (Pt 5:521-528).

The activity of delta-aminolaevulinic acid dehydratase (ALA-D:porphobilinogen synthase) was measured in whole blood from a group of workers with acute exposure to lead and with low blood lead levels, a group of workers with chronic lead exposure and high blood lead levels, and a group of people without undue environmental lead exposure. The activity of ALA-D was reduced significantly at low blood lead levels only if undue exposure to lead had occurred, and was thus a reflection of low level lead poisoning. In chronic lead exposure, the enzyme was not invariably reactivated fully with dithiothreitol, indicating

more severe enzyme poisoning. The one lead worker with symptomatic lead poisoning had the most marked enzymesuppression. Measurement of both ALA-D activity and blood lead levels was more useful than the measurement of blood lead levels alone in the diagnosis and assessment of the severity of lead poisoning.

SYMPTOMS OF LEAD POISONING

<u>MILD</u>	<u>MODERATE</u>	<u>SEVERE</u>
Abdominal Discomfort	Anxiety	Confusion
Decreased Appetite	Arthralgia	Disorientation
Fatigue	Colic	Dizzy Spells
Headache	Concern	Personality Change
Metallic Taste	Constipation	Tremulousness
Nausea	Decreased Concentration	
Nervousness	Decreased Sexual Drive	
Sick Feeling	Diarrhea	
	Insomnia	
	Myalgia	
	Shakiness	
	Vomiting	
	Weakness	

B. DIAGNOSIS OF LEAD INTOXICATION**1. Signs and Symptoms**

The usual signs and symptoms associated with clinical lead intoxication are summarized in the description of the severity of lead intoxication.

Lead poisoning is a rather specific disease and diagnosis should not be made by exclusion, that is, solely on the basis of a history of exposure to lead and evidence of increased absorption in the absence of any other explanation. The diagnosis should be based on clinical signs and symptoms and on significant biochemical changes in addition to an adequate history of lead exposure and evidence of increased absorption. While blood lead measurements are valuable in confirming exposure, estimating absorption and evaluating effects, they cannot be diagnostic by themselves since there is no blood lead level pathognomonic of lead intoxication. Increased amounts of lead may be present in the blood without clinical effects. Blood lead constitutes a useful biological monitor in determining current absorption and signaling the need for corrective measures, but the guidelines which indicate acceptable blood levels cannot be extrapolated to diagnose lead intoxication.

The frequency of abnormal clinical findings in lead workers is shown for the ten most common signs and symptoms. The

frequency of involvement was greatest at smelter plants and least at chemical plants. The most prevalent complaint was colic followed by general gastrointestinal symptoms and anorexia. Note that objective tremor was infrequently seen as was extensor muscle weakness. Workers who reported symptoms consistent with lead intoxication had significantly higher blood lead levels than workers at the same plant who were asymptomatic.

Table 2 Frequency of abnormal clinical findings in lead workers at 3 plants—United States, 1975, 1976

Findings	Tennessee Smelter (78)†	Utah Smelter (79)†	Missouri Chemical plant (33)†
Fatigue	19 (24%)	8 (28%)	19 (66%)
Colic	13 (17%)	19 (64%)	1 (3%)
Gastrointestinal symptoms*	17 (22%)	16 (62%)	3 (6%)
Anorexia	11 (14%)	12 (41%)	—
Myalgia	13 (17%)	7 (24%)	6 (11%)
Joint pain	21 (28%)	4 (14%)	10 (19%)
Objective tremor	2 (3%)	4 (14%)	2 (4%)
Extensor muscle weakness	10 (13%)	0	2 (4%)
Possible encephalopathy	0	2 (7%)	0
Anemia	12 (15%)	11 (38%)	4 (8%)
BUN elevation	4 (5%)	3 (11%)	17 (32%)

*Includes nausea, vomiting, diarrhea, and constipation.
†Number of workers studied.

Other factors related to symptoms following exposure to lead in the workplace: a high medical consultation rate was noted among lead workers during the industrial dispute over the possible effects of lead in a printing establishment. The rates were higher than the non-lead exposed persons; however, when the lead workers were divided into groups based on the blood lead ALA or ALA-D levels, no significant difference was found between the numbers of consultations. It was concluded that the industrial confrontation might have been a major cause of the high consultation rate of lead workers.

2. Biologic Monitoring Data

The measurement of the concentration of lead in the blood is the most widely used measure of lead absorption. At levels of 50 ug of lead per deciliter and below, symptoms of lead intoxication are unlikely to be present. They are in fact rare at concentrations as high as 65 ug/dL.

The mean blood lead concentrations at which specific symptoms associated with lead absorption occur, based on a study of smelter workers in Tennessee are shown below.

Symptom	Mean Blood Lead ug/dL
Gastrointestinal	
Present	101
Absent	66
Abdominal Pain	
Present	101
Absent	68

<u>Symptom</u>		<u>Mean Blood Lead ug/dL</u>
Neuromuscular	Present	94
	Absent	66
Anorexia	Present	94
	Absent	66
Joint pains	Present	92
	Absent	66
Constitutional Complaints	Present	88
	Absent	63

When persons are symptomatic at lower blood lead concentrations it may be because of previously increased body burdens. The provocative chelate test can be used to indicate body burdens from previous exposures. In addition to measurement of blood lead other indices include measurement of lead in the urine, hair, nails, teeth and bones.

The "No Detect Effect Level" in terms of Pb B as judged by WHO in 1977 appears below.

<u>No Detected Effect Level</u>	<u>Effect</u>	<u>Population</u>
<10	Erythrocyte ALAD inhibition	Adults, children
20-25	FEP	Children
20-30	FEP	Adult, female
25-35	FEP	Adult, male
30-40	Erythrocyte ATPase inhibition	General
40	ALA excretion in urine	Adults, children
40	CP excretion in urine	Adults
40	Anaemia	Children
40-50	Peripheral neuropathy	Adults
50	Anaemia	Adults
50-60	Minimal brain dysfunction	Children
60-70	Minimal brain dysfunction	Adults
60-70	Encephalopathy	Children
>80	Encephalopathy	Adults

3. Clinical Laboratory Tests

(a) Blood and blood precursors:

A variety of tests are available to measure the effects of lead on body systems. Those which interfere with the hematopoietic index include:

Hemoglobin - hematocrit

Blood ALA

Erythrocyte ALA-dehydratase activity

Erythrocyte non-heme iron
 Erythrocyte protoporphyrin
 Erythrocyte zinc protoporphyrin
 Reticulocytes (immature erythrocytes)
 Punctate basophilia ("stipple cells")
 Erythrocyte life span (increased fragility)
 Urinary index:
 delta-Aminolevulinic Acid (ALA)
 coproporphyrin
 uroporphyrin
 porphobilinogen
 Hematopoietic Index

The exposure-responses between blood lead, ALA and FEP are shown in Figure 6.

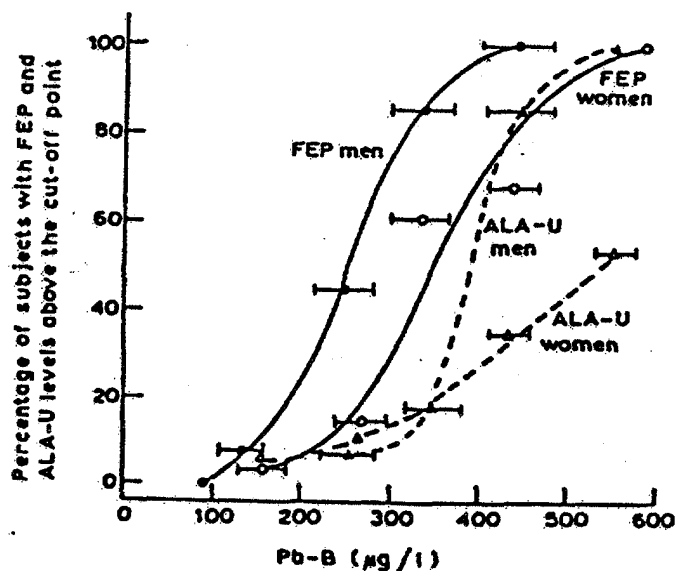


Fig. 6 Exposure-response curves for PbB and the percentage of subjects (men and women) with free erythrocyte protoporphyrin (FEP) and ALA-U levels above cut-off point. For women, the cut-off points for FEP and ALA-U were 826 µg/l of erythrocytes and 5.44 mg/g of creatinine, respectively; for men, the cut-off points for FEP and ALA-U were 708 µg/l of erythrocytes and 4.76 mg/g of creatinine, respectively (From WHO, 1980).

VI B3

Marcus, A.H., Schwartz, J.
Dose response curves for erythrocyte protoporphyrin
versus blood lead effects of iron status.
Environmental Research, 1987, Dec., 44(2):221-7.

An increase in erythrocyte protoporphyrin (EP) is one of the most useful indicators of adverse biological response to lead exposure. A nonlinear mathematical model relating EP to blood lead concentration (PbB) was fitted to data in a sample of 1577 U.S. children (ages 2-6) in the Second National Health and Nutrition Examination Survey (NHANES II). Iron status was defined by percentage transferrin saturation (PTS). The dose-response curves for EP vs PbB increased systematically with decreasing PTS, largely due to decrease of a parameter proportional to red cell lead holding capacity with decreasing PTS.

Braithwaite, R.A., & Brown, S.S.
Clinical and sub-clinical lead poisoning:
a laboratory perspective.
Human Toxicology, 1988 Sep. 7(5):503-13.

The background, scope and limitations of laboratory methods for the diagnosis of inorganic lead poisoning are outlined in the context of the work of a specialist clinical laboratory for trace element analysis. Data for blood lead, hemoglobin and erythrocyte zinc protoporphyrin concentrations are presented in cases of clinical and sub-clinical poisoning due to accidental, or occupational exposure. Data from population surveys of children and adults subject to either environmental or occupational exposure are also shown. In general, analysis for lead in an appropriate specimen of blood offers the single most useful index of exposure. The importance of good accuracy control in such measurements is emphasized.

VI B3 C

Holdstein, Y. et al.
Auditory brainstem evoked potentials in asymptomatic,
lead-exposed subjects.
Journal of Laryngology & Otology, 1985, Sep,
100(9):1031-6.

Auditory brainstem Evoked Potentials (ABEPs) were recorded from 29 adults and children, accidentally exposed to lead through food until approximately a year prior to this study. ABEPs were recorded in response to 75 dBHL clicks presented at rates of 10/second and 55/second. Average values were calculated for peak latency and for interpeak latency differences. Average values of the effect of increasing stimulus rate were calculated as well. Similar values were calculated for normative child and adult control groups. IPLD(I-III) showed the most significant

and recurring results, with longer intervals in lead-exposed children compared with their control group. Increasing the stimulus rate, on the other hand, affected the adult lead-exposed subjects more than the children. These results may imply an impairment of the peripheral portion of the auditory system with axonal and myelin involvement. ABEP is suggested as a sensitive detector of clinical lead exposure effects on the nervous system.

Pollock, C.A., & Ibels, L.S.

Lead intoxication in Sydney Harbour Bridge workers.
Australian & New Zealand Journal of Medicine, 1988,
Feb, 18(1):46-52.

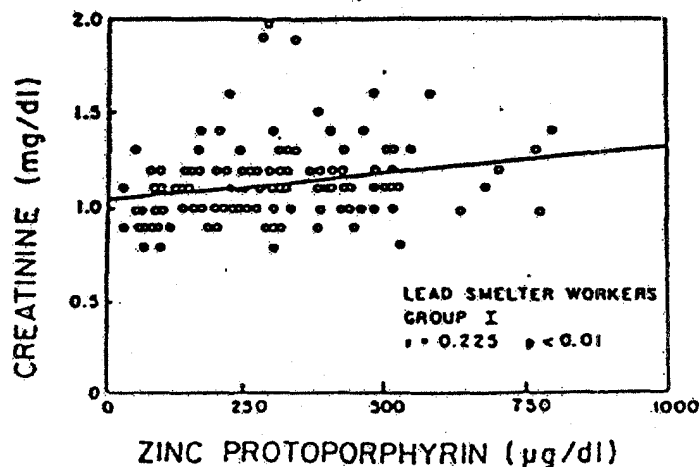
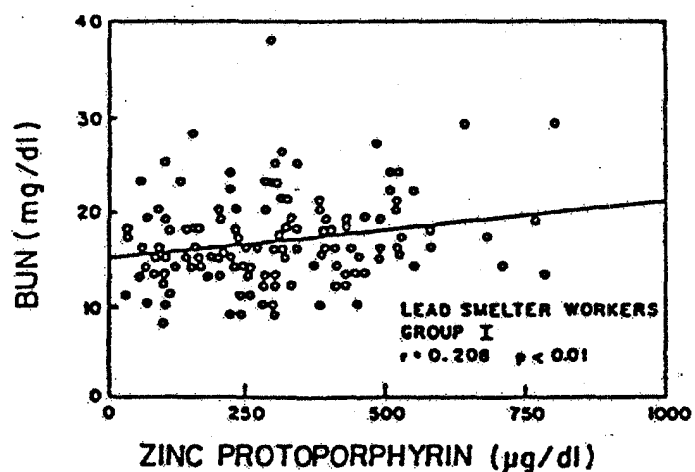
Thirty eight Sydney Harbour Bridge workers were assessed for possible lead intoxication. Forty seven percent were found to have significant lead intoxication as assessed by calcium disodium adetate chelation (Ca EDTA) testing and were subsequently effectively and safely treated with Ca EDTA. The prevalence of neurological, constitutional, gastrointestinal and musculoskeletal symptoms was significantly greater in those with, than those without lead toxicity. Although blood lead levels and, to a lesser extent, hematological parameters, were of some use in diagnosis, they were not sufficiently sensitive and thus should not be used in screening workers who are at risk of lead intoxication. Ca EDTA remains the diagnostic method of choice. Patients exposed to lead dust and fumes, in whom symptoms of lead intoxication are present, should undergo such testing and, if a positive result is obtained, then EDTA chelation therapy should be instituted.

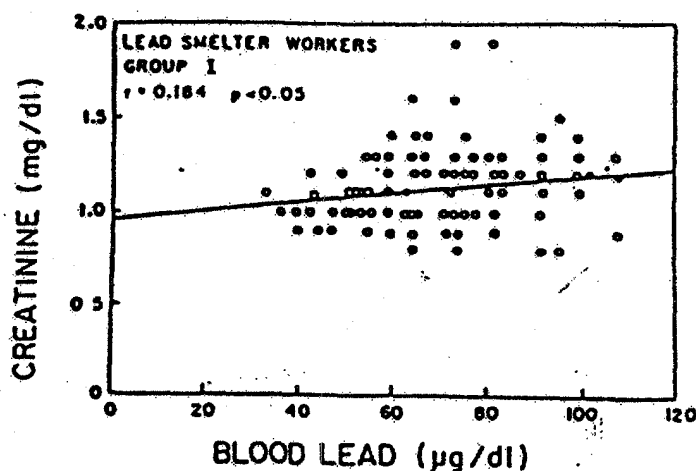
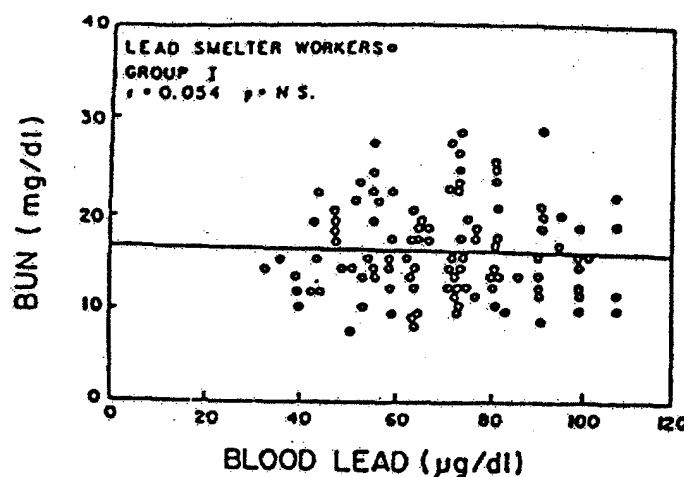
(b) Urinalysis:

Analysis of urine for its lead content can be used to estimate the concentration of lead in the urine. A ratio of mean UPb/BPb is 1.4. The routine urinalysis should be conducted at the time of the periodic medical examination, though changes in protein excretion are rare and formed elements are not generally increased.

(c) Other evaluations:

1) Blood chemistry panels should be measured with special attention to the values for BUN and creatinine. The relationship between these two substances and the concentration of lead in the blood are shown in the following graphs.





2) Measurements of glomerular filtration (GFR) rates are recommended.

3) The measurement of N-Acetyl B-D-Glucosaminidase (NAG) may be of assistance in measuring early kidney damage though it has not as yet been correlated with other measurements of kidney function.

4) Nerve conduction tests

5) Bone density measurements

C. TREATMENT

1. Symptomatic

Any persons displaying signs or symptoms of over exposure to lead should be removed from further exposures. Symptoms should be treated as required and fluid balance maintained. Procedures for reducing the body burden of lead in the soft tissue are as follows:

- Decrease respiratory exposure
- Decrease absorption from the gut
- Increase excretion in the urine
- Increase excretion in the bile
- Increase deposition in the bone

The procedure most widely used is the removal from exposure. At times chelation is required.

Chelation is the process by which the binding of heavy metal cations, including lead to body ligands can be reversed. A

chelate is the complex formed between the metal and the compound containing two or more potential ligands.

The effectiveness of a chelating agent depends on:

- (a) The relative affinity of the chelation for the metals as compared to essential body metals;
- (b) The distribution of the chelater in the body;
- (c) The mobilization of the chelate;

There are three agents which are used most frequently: BAL, EDTA and Penicillamine. A new chelator, DMSA, has obtained FDA approval as an investigational new drug (IND).

In addition to reducing the soft tissue concentrate of lead, chelation also reduces the tissue concentration of other trace metals; becomes less effective on continuous administration; requires parenteral administration except for Penicillamine and DMSA; increases absorption of lead from the gut when taken orally in the presence of increased lead in the gut. The dosage schedule for these drugs is as follows:

Drug	Dose	Route	Contra-indications
BAL	18 mg/kg/24 h for 2 days 12 mg/kg/24 h for 1 day 6 mg/kg/24 h for 7 days	Deep intra-muscular	Hepatic disease
Ca-EDTA	50 mg/kg/24 h for 5 days Allow 2 days before starting a second course	Intravenous or intramuscular	Kidney disease
D-Penicillamine	0.9-1.5 g/24 h	Oral	Kidney disease

The beneficial and possible adverse effects of chelation therapy in man are as follows;

<u>Category</u>	<u>Observed Effect</u>
Beneficial:	Increased excretion of lead from the body and/or reduction in blood lead levels. Decrease in symptoms following treatment. Therapy is generally well tolerated.

VI C

Cory-Slechta, D.A. & Weiss, B.
 Efficacy of the chelating agent CaEDTA in reversing lead induced changes in behavior.
 Neurotoxicology, 1990 Winter, 10(4):685-87.

The chelating agent CaEDTA has been reported to reverse the deficits in intellectual function and performance associated with Pb (lead) exposure in children. However, such studies have not included rigorous controls for the intervention procedures per se. The experiments reported here examined reversibility of performance changes in a rat model based on behavior sensitive to low-level Pb exposure. Rats were exposed to 50 ppm sodium or Pb acetate in drinking water from weaning. Performance maintained under a Fixed-Interval schedule of food reinforcement began at 55 days of age. Following the onset of the characteristic increase in short inter-response times (IRTs) associated with low-level Pb exposure after 35 experimental sessions, Pb treatment was terminated. Animals within both the control and Pb groups then were matched on the basis of performance indices and injected daily for five days with either saline, 75 mg/kg, or 75 mg/kg, or 150 mg/kg CaEDTA. Subsequent changes in FI performance were monitored for 35-60 sessions. No consistent effects of CaEDTA were detected in control animals. CaEDTA treatment failed to reverse the behavioral effects in Pb-exposed animals. If anything it tended to further increase the proportion of short IRTs. These data suggest that better controlled clinical studies are warranted to evaluate the efficacy of CaEDTA in reversing Pb-induced behavioral effects before its application for these purposes becomes widespread.

Fournier, L. et al.
 2,3-Dimercaptosuccinic acid treatment of heavy metal poisoning in humans.
 Med. Toxicol. Adverse Drug. Exp. 1988 Nov-Dec 3(6):499-504.

Fourteen patients with heavy metal poisoning received 2,3-dimercaptosuccinic acid (DMSA). Twelve subjects were given 30 mg/kg/day for five days. One subject was started on a lower dose because of a history of atopy; another subject was treated for fifteen days because of a very high initial blood lead concentration. In the nine subjects who had lead poisoning, DMSA decreased blood lead concentrations by 35 to 81% and induced a 4.5-16.9-fold increase in mean daily urinary excretion of the metal. In the acutely arsenic poisoned case, the plasma arsenic concentration on day seven was half the pretreatment value, while no clear decrease was observed in a chronically exposed subject. In three mercury cases, DMSA increased daily mercury urinary excretion 1.5, 2.8 and 8.4-fold, respectively while blood mercury concentrations remained below detection limits. No serious side effects were observed and three weeks after administration of the drug, the clinical condition of all

subjects was either stable or improved. These results indicate the efficacy of DMSA for lead poisoning in humans and provide a rationale for further investigating its usefulness in mercury and arsenic poisoning cases.

VI C

Baer, R.D. & Ackerman, A.
Toxic Mexican folk remedies for the treatment of empacho in the case of azarcon, greta and albayalde.
Journal of Ethnopharmacology, 1988, Sept. 24(1):31-9.

This article discusses the availability of three lead-based sales which are being used as folk remedies in Mexico. Distribution systems and geographic availability were determined and purchased samples were found to be very high in lead content. The findings suggest the need for further research to understand the reasons why such remedies are chosen, and the development of an educational program to discourage their use.

Calabrese, E.J. et al.
The effects of vitamin C supplementation on blood and hair levels of cadmium, lead and mercury.
Annals of the New York Academy of Sciences, 1987, 498:347-53.

Fifty two adult male subjects were randomly assigned to one of three possible treatment groups: supplemental ascorbic acid at one of two levels, 500 mg or 1000 mg, or a placebo. Hair and blood samples were taken before vitamin C or placebo supplementation was started and at monthly intervals thereafter for three months. Samples were analyzed for cadmium, lead and mercury. Results indicate that vitamin C did no significantly effect levels of these metals in either hair or blood samples.

The distribution of tissue lead in persons with no exposure and those with severe exposure is shown in the following table. Note the ratios range from approximately four to twenty times as great in those with severe exposure.

	Individuals with No Exposure (mg/100 g tissue)	Individuals with Severe Exposure (mg/100 g tissue)
Kidney	0.05	0.22
Liver	0.12	0.71
Spleen	0.03	0.86
Muscle	0.03	0.10
Lungs	0.03	0.08
Brain	0.04	0.35
Flat bones	0.65	13.00
Long bones	1.78	8.00

D. THE METABOLISM OF LEAD

The metabolism of lead following oral intake and inhalation was studied intensely by Kehoe and his co-workers at the Kettering Laboratories.

ORAL AND INHALATION LEAD EXPOSURESIN HUMAN SUBJECTS - 1937-72

EXPOSURE	SUBSTANCE ANALYZED	MEDIAN ug
NORMAL	DIET (1937)	300 ^a
	DIET (1972)	100 ^a
	DIET (1937-72)	159 ^a
	BLOOD	25 ^b
	URINE	29 ^c
	FECES	196 ^a
INGESTION 300-3000 ug/day	BLOOD	0.017 ^d
	URINE	0.045 ^d
	FECES	0.83 ^d
	BALANCE	0.133 ^d
INHALATION 10-150 ug/H ³	BLOOD	0.57 ^{be}
	URINE	1.41 ^{ce}
	FECES	1.47 ^{ae}

a - total

b - ug/dL

c - ug/L

d - ug/for each 1.0 ug of lead in diet per day

e - ug/for each 1.0 ug/H³ in the air

E. EXCRETION

Ninety percent of ingested lead is eliminated unabsorbed through the feces. Absorbed lead is excreted primarily in the urine (about 76%); in the feces about 16%; 81/2% in the hair, sweat and nails. Human milk may contain up to 12 ug/L. Persons with no known high exposure to lead have an average excretion of 12ug/L.

F. STORAGE

Accumulation of lead in the body begins before birth and continues throughout life. The total of that body burden for adults ranges from about 60 to 140 mg. Most absorbed lead is eventually deposited in the skeleton, which accounts for over 90% of the body burden of lead. Seventy percent is in dense avascular bone and is thus considered to be biologically inert. The amount of skeletal lead is greater for males than for females and bone lead concentration increases with age, although blood lead usually remains stable.

<u>Age in Years</u>	<u>Lead ppm Bone Ash</u>
0-1	<1
2-10	2.5
20-30	16.8
31-40	43.1
80	22.0

The concentration of lead in bone may be determined by a non-invasive technique neutron activation (finger) or by biopsy.

The B-Pb decay fits well with a two-compartment system; the fast compartment has a time of 50% retention $T_{1/2}$ of 38 days; the slow compartment, 5 to 6 years.

The ratio of lead in the fibula to that in the vertebral bone $FiPb/VePb$ is higher in ex-lead workers than current ones.

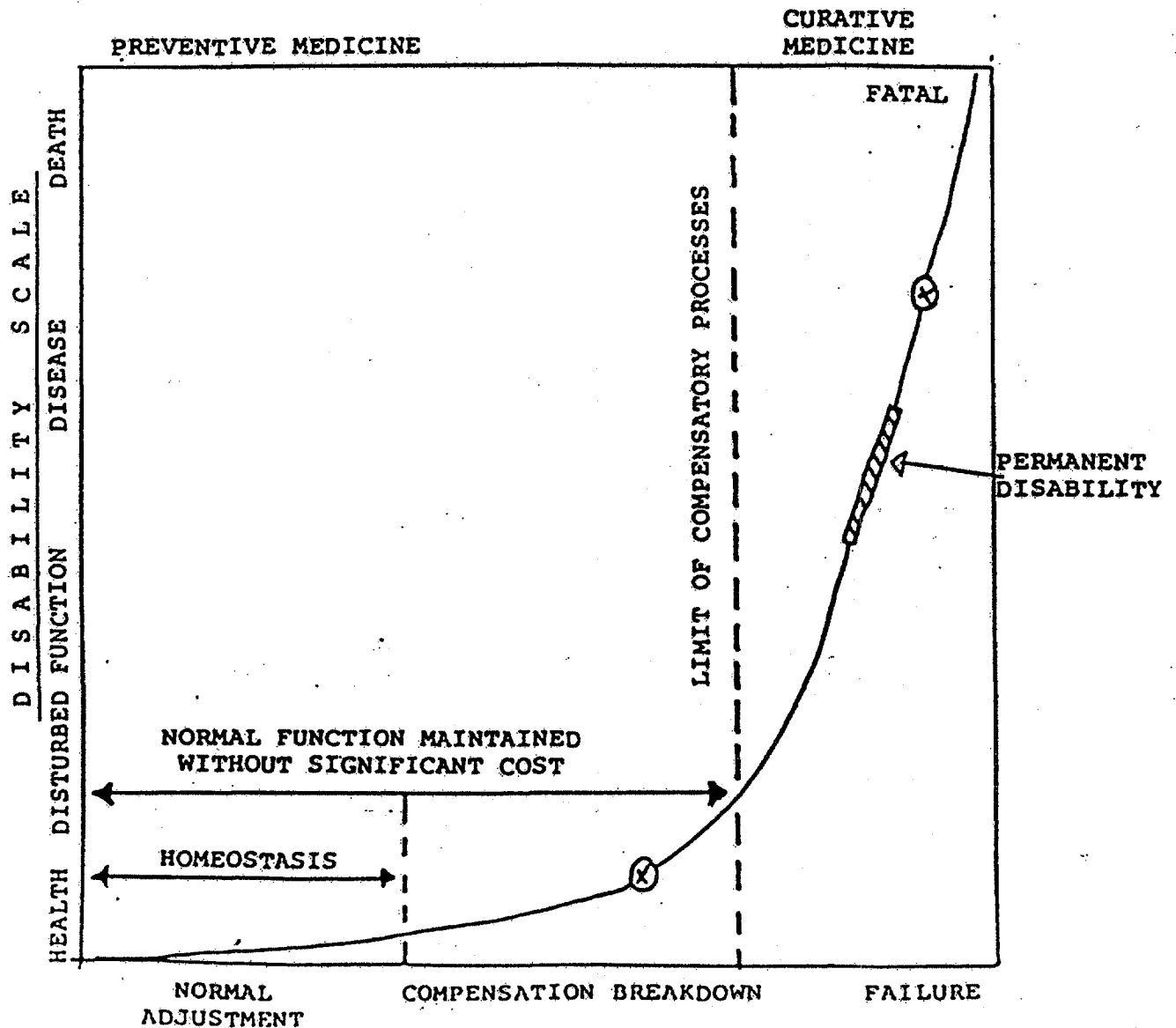
A number of other metals are retained in the body. The concentration of these in the normal kidney of unexposed persons is as follows:

<u>Metal</u>	<u>Median Value ppm (kidney ash)</u>
Pb	110
Al	23
Cd	1400
Au	3

Noise
 Climate
 Chemical Factors
 Mental Stress
 Microbiologic Factors
 Social Factors

F. Recognizing the many factors which contribute to maintenance of normal function, Hatch suggested the following diagram depicting health and impairment.

IMPAIRMENT SCALE



IV. BIOLOGIC EFFECTS

A. BLOOD FORMING ORGANS

Lead has profound effects on a number of steps in the synthesis of hemoglobin from its precursors. Changes in the rate of synthesis leads to a reduction in the amount of hemoglobin and numbers of red cells. A schematic representation appears in the following figure.

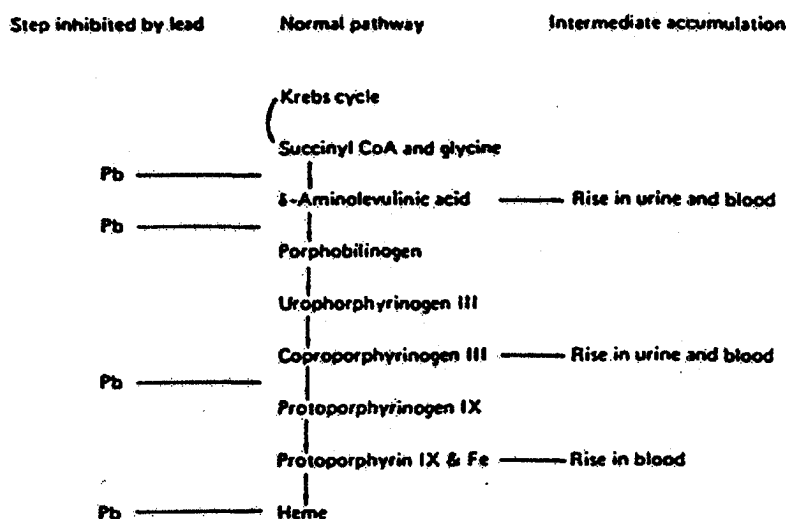


FIG. Modified from Chisola

Note the four steps at which lead effects the formation of hemoglobin. As a result there is an increase in the precursors in the plasma and urine, especially of ALA, coproporphyrin III, protoporphyrin IX and serum iron. There is also a related increase in the free erythrocytic porphyrin (FEP), and zinc protoporphyrin.

Reticulocytosis and decreased red cell osmotic fragility may also occur, but basophilic stippling is no longer considered to serve a useful role in diagnosis. As serum iron is elevated, there results ferruginous micelles and aggregation of ferritin in mitochondria. Ringed sideroblasts appear in bone marrow.

IV A

Grandjean P; et al.

Delayed blood regeneration in lead exposure: an effect on reserve capacity.

Am J Public Health, 1989 Oct, 79(10): 1385-1388.

Twenty-five lead exposed Danish battery production workers and 25-age-matched controls were examined to evaluate subclinical effects on blood formation. Blood lead levels averaged 2.14 $\mu\text{mol/L}$ and 0.35 $\mu\text{mol/L}$ in two groups; the lead workers also showed high levels of erythrocyte protoporphyrin, as compared to the controls. Otherwise, the hematological parameters indicated an appropriate iron status and not other deviations. From all subjects, 0.15 L of blood was bled as part of a normal blood donation. Five and eleven days later, reticulocyte counts were significantly higher in the control group than in the lead-exposed workers. On day 15, the lead workers showed a significant delay in blood regeneration, as evidenced by lower hemoglobin concentration, and erythrocyte and reticulocyte counts. The lead exposure in the present study was within legal limits, and lead induced anemia would be expected only at much higher exposure levels. Thus, despite the normal hematological findings in the initial examination, the lead exposure caused a decreased reserve capacity for blood formation, and this effect became evident only after the blood loss.

Poulos L; et al.

Statistically significant hematopoietic effects of low blood lead levels.

Archives of Environmental Health, 1986 Nov-Dec, 41(5): 384-386.

Look up
for

Blood lead (Pb-b) concentrations, hematocrit (Ht), and hemoglobin (Hb) were determined in three groups of men working in different parts of a cable-producing factory. All three parameters examined, i.e., Pb-b, Ht, and Hb, in the above groups were found to be within "normal" limits. However, within each group of men studied, there was a statistically significant negative correlation between Pb-b concentrations and Ht and Hb values. This finding indicates that any increase in Pb-b concentration, even within the "normal" values, may result in a decrease of hematocrit and hemoglobin values of the same subjects.

Ken R; et al.

An evaluation of the hypothesis that females are more susceptible than males to lead induced hematological alterations.

Human Toxicology, 1988 Mar, 8(2): 105-109.

1. A retrospective epidemiological study was conducted to

assess the hypothesis that sex differences exist with respect to selected lead-induced red blood cell parameters. The study utilized data previously collected in the Boston Childhood Lead Poisoning Prevention Program.

2. This study revealed no statistically significant difference between males and females (n-1518) aged 1-5 years for blood FEP levels when blood lead levels were similar.

3. These findings are in contrast with previously published research with human adults, which has suggested that adult females display significantly greater FEP values at identical blood level values as similarly aged men.

B. BLOOD LEAD EFFECTS THE CIRCULATION OF LEAD IN RED BLOOD CELLS AS FOLLOWS:

- Accumulation in the red blood cell increases
- Osmotic resistance increases
- Mechanical fragility increases
- Loss of potassium occurs
- Sodium and potassium ATPase activity decreases
- Life span is decreased
- Basophilic stippling occurs

Abnormal hemoglobins may effect lead retention:

In Glucose-6-Phosphate dehydrogenase deficiency there is an increased retention of lead in children but not in adults.

In cases of B-Thalassemic trait, adult blood leads are higher than those without the trait.

No statistically significant relationship occurs between the lead concentration of umbilical cord blood levels and prenatal residency in the urban and suburban infants. Nor is there a relationship between smoking and the blood-lead concentration.

Black children with a deficiency in glucose-6-phosphate dehydrogenase have a higher concentration of lead in the blood than the non-deficient.

C. GASTROINTESTINAL TRACT

Common symptoms of lead intoxication include anorexia, nausea, vomiting, diarrhea, constipation and most typically, colic. These are secondary to spasmotic smooth muscle contraction in the intestinal wall. The mechanisms involved are not well understood. Colic rarely occurs today among industrial workers.

On the other hand, it occurs frequently in leaded children. X-rays of the abdomen are of help in identifying paint chips containing lead in children with pica.

D. KIDNEY

Renal function disturbances caused by increased quantities of lead ingested by children are those seen in the Fanconi

III A

Lilley SG; et al.

The use of sweat to monitor lead absorption through the skin.

Sci Total Environ, 1988 Oct 15, 76(2-3): 267-78.

It is usually assumed that lead can be absorbed through the skin only if it is present as an organolead compound such as tetraethyllead or lead maphthanate. It has been found, however, that lead nitrate solution placed on the skin results in rapid absorption of lead, and transport of the metal around the body. The absorbed lead appears in sweat and saliva, but not in blood or urine. The application of 6 mg of lead as 0.5 M lead nitrate to the left arm resulted in an increase in lead concentration in pilocarpine-induced iontophoresis sweat samples taken from the right arm, an initial value of 15-25 micrograms Pb1-1 to greater than 300 micrograms Pb1-1 after 2 days. Saliva lead increased from 2.5 - 15 micrograms Pb1-1 in the same period. The rate of lead absorption through the skin increases with increased sweating of the skin. Since no measurable increase in blood lead has been found, the lead must be transported in the plasma and rapidly concentrated into the extracellular fluid pool (sweat and saliva), without significant uptake by the erythrocytes, and with a very low transient concentration in the plasma. Workers occupationally exposed to lead have extremely high levels of lead in sweat even though their lead in blood is only moderately elevated. Lead absorbed through the skin may be eliminated via sweat and other extracellular fluids, and hence not be as great a health hazard as ingested lead, but this will need to be proved by further studies.

II B

Lolin Y; O'Gorman P.

An intra-arythrocytic low molecular weight lead-binding protein in acute and chronic lead exposure and its possible protective role in lead toxicity.

Annals of Clinical Biochemistry, 1988 Nov, 25(Pt 6): 688-697.

A low molecular weight protein was measured in erythrocytes from workers with chronic and recent lead exposure, with and without clinical lead toxicity, and from a group of control subjects not exposed to undue environmental lead. The protein was detected in all the workers, but in significantly smaller amounts in those with symptoms, and was absent from controls. The synthesis of the protein is induced at blood lead concentrations above 1.9 mumo/L, but is reduced in workers susceptible to clinical lead toxicity at blood lead concentrations below 1.0 mumo/L. The activity of the red blood cell dithiothreitol (DTT)--activated-5-aminolesvulinate

dehydratase (ALA-D) was correlated with the concentration of low-molecular-weight protein, with both being particularly low in the symptomatic workers. Previous studies have shown that the protein binds lead. By sequestering excess lead into a non-toxic form, the protein may have a protective role in preventing clinical, and reducing biochemical, lead toxicity.

Syndrome. This is characterized by aminoaciduria, glucosuria and hyperphosphaturia, and is rarely seen in adult cells. Long-term exposure to lead may give rise to irreversible functional, and morphological, renal changes. These consist of an intense interstitial fibrosis, tubular atrophy and dilatation; an increased tubular cell proliferation also occurs. Little is known about the dose-effect or dose-response of nephrotoxicity from inorganic lead. The WHO Task Force suggests that prolonged exposure to 70 ug/L may produce this. Lower estimates of the concentration necessary to produce these are given by others. The problem in predicting impending kidney damage is the relative insensitivity of the increase in concentration and rise of creatinine and BUN in the serum as a measure of decreased renal function. There is still controversy as to whether exposure to lead in childhood will result in nephropathy in later life. One such study, by Emmerson, was positive. Another in the United States was negative. Lead nephropathy is divided in two phases. The earliest phase lasts from days to months. It is associated with acute, repeated clinical manifestations of lead poisoning. Chronic lead nephropathy, on the other hand, occurs only after years of exposure and is associated with severe changes in renal structure, failure of function, and at times hypertension and gout. The incidence of gout is much higher in chronic lead nephropathy than in other types of chronic renal disease.

There are two principal stages of lead-induced cellular histologic alteration in the kidney. In stage one, intranuclear inclusion bodies and alterations of mitochondrial morphology appear but are reversible. In stage two a chronic condition occurs characterized by interstitial fibrosis, tubular atrophy, dilatation of the tubules and arteriosclerotic changes.

Wedeen, in 1975, was the foremost in pointing out that occupational lead nephropathy had rarely been recognized in the United States. In his studies he concluded that as many as 10 percent of the work force who in the past had worked with lead would develop advanced stage renal disease.

Tubular proteinuria is not an early manifestation of toxicity due to industrial lead exposures. Apparently, there is no problem in the renal handling of low hypermolecular-weight proteins, and the protein tubular reabsorption mechanism appears to be intact. Nor is there evidence of permeability to microglobulins. As the degree of injury to the tubules increases, a proteinuria appears which is of a relatively small quantity. There also can be identified a number of enzymes released from the tubules as well as brush border cells.

As the blood lead and FEP increase, there is a proportional increase in the concentrations of BUN and creatinine in the serum.

Studies Relating Lead Exposure and Kidney Disease

STUDY	SUBJECTS	EXPOSURE	OUTCOME
Dickinson 1881	42 men	occupational	26 with chronic interstitial nephritis
Purdy, 1886.	42 men	occupational	2/3 with granular kidneys
Nye 1929	34 m & f	severe childhood poisoning	29 with chronic nephritis
Blackman 1936		ingestion, childhood exposure, few months to years	renal changes: inclusions bodies in proximal renal tubules
Henderson 1954	401 children	ingestion	108 deaths from hypertension or nephritis
Danilovic 1958	12 families	lead contaminated flour	37 deaths from chronic nephritis, 23/44 living with renal disease
Emmerson 1960	23 adolescents	ingestion	4 patients with increased lead excretion after chelation
Radošević 1961	53 subjects	occupational or environmental	2/53 with chronic nephropathy, 23/53 with functional renal impairment
Emmerson 1963	32 children	ingestion	32 patients with increased lead excretion after chelation
Emmerson 1963	19 controls 22 cases 23 renal pts	none, ingestion	controls with normal lead excretion, lead intoxicated pts with increased excretion, renal pts with normal excretion

IV D

Sampson B; et al.

- * Survey of blood lead and plasma aluminum concentrations in patients of a renal unit. Nephrology, Dialysis, Transplantation, 1989, 4(5): 375-381.

Blood lead and plasma aluminum concentrations have been measured in patients with end-stage chronic renal failure treated by hemodialysis (HD) or by continuous ambulatory peritoneal dialysis (CAPD) and in a control group of non-dialysed patients with chronic renal failure (CRF). Data on a group of subjects with normal renal function is included for comparison. We have found significantly increased mean blood lead and plasma aluminum concentrations in all patients with chronic renal failure compared to a group with normal renal function. All blood lead concentrations were within the accepted safe exposure range of less than 1.8 $\mu\text{mol/l}$ (380 micrograms/l). There were significant differences among the patient groups: home HD, $0.60 \pm 0.25 \mu\text{mol/l}$ (124 ± 52 micrograms/l); hospital HD, $0.39 \pm 0.31 \mu\text{mol/l}$ (81 ± 61 micrograms/l); CAPD, $0.32 \pm 0.17 \mu\text{mol/l}$ (66 ± 35 micrograms/l); CRF, $0.38 \pm 0.20 \mu\text{mol/l}$ (79 ± 41 micrograms/l); normal, $0.24 \pm 0.11 \mu\text{mol/l}$ (50 ± 23 micrograms/l). Correction of the blood lead results for hemoglobin accentuates these differences (i.e. hospital HD, $1.61 \pm 3.25 \text{ nmol/g}$ (0.86 ± 0.67 micrograms/g); CRF, $3.05 \pm 1.46 \text{ nmol/g}$ (0.63 ± 0.30 micrograms/g); normal, $1.65 \pm 0.70 \text{ nmol/g}$ (0.34 ± 0.14 micrograms/g). Plasma aluminum concentrations show a similar pattern: home HD, $1.09 \pm 0.70 \mu\text{mol/l}$ (29.1 ± 18.9 micrograms/l); CAPD, $0.34 \pm 0.31 \mu\text{mol/l}$ (9.2 ± 9.2 micrograms/l); CRF, $0.18 \pm 0.09 \mu\text{mol/l}$ (4.9 ± 2.1 micrograms/l) normal; $0.09 \pm 0.07 \mu\text{mol/l}$ (2.4 ± 1.9 micrograms/l). (Abstract truncated at 250 words)

Huang JX; et al.

- * Observations on renal function in workers exposed to lead.

Sci Total Environ, 1988 Jun 1, 71(3): 535-537.

Renal function was studied in 10 workers chronically exposed to lead at a smelter. The geometric means of lead were 10 (range 19-115) micrograms/g creatinine or 71 (range 20-250) micrograms/l in urine, respectively. There were no significant differences between the lead-exposed group and a control group in the concentrations of beta 2-microglobulin in serum, urinary total protein and IgG, whereas the level of beta 2-microglobulin in urine was significantly higher in the lead-exposed group (p less than 0.01). No individual lead worker showed abnormally increased level of urinary beta 2-microglobulin. The significance of increased excretion of

beta 2-microglobulin on the basis of the group remains to be elucidated.

Greenberg A; Parkinson DK; et al.
Effects of elevated lead and cadmium burdens on renal function and calcium metabolism.
Archives of Environmental Health, 1986 Mar-Apr, 4(2): 69-76.

To assess the pathophysiologic significance of increased body burdens of lead and cadmium, detailed renal function studies and evaluation of calcium, phosphorus, and vitamin D metabolism were carried out in 38 industrial workers exposed to lead and cadmium for 11 to 37 years. Body burden of lead, as assessed by X-ray fluorescence measurement of tibia lead content, was elevated in 58% of the men and, when assessed by excretion of lead after Ca-EDTA infusion, was elevated in 36%. Liver or kidney cadmium burden, as assessed by neutron activation analysis, was elevated in 31%. Creatinine clearance was normal in all workers. One worker was hyperuricemic and two were proteinuric; three had increased beta 2-microglobulin excretion and one had diminished urinary acidifying ability. Maximal urinary concentrating ability was abnormal in a significant fraction, i.e., 52% of the men. Individuals with a high lead burden had a slight decrease in mean serum phosphorus but no accompanying phosphaturia. There was no abnormality of serum calcium. Twenty-two percent of subjects were hypercalciuric and two had low Vitamin D levels, but these abnormalities bore no relation to heavy metal burden. In this carefully characterized group of men with chronic lead and calcium exposure, definite, if subclinical, effects on renal function and serum phosphorus but not calcium or vitamin D metabolism were demonstrable.

✱ Van de Vyver FL; et al.
Bone Lead in dialysis patients.
Kidney International, 1988 Feb, 33(2): 601-607.

We measured lead and cadmium in multiple bone biopsies from 11 cadavers without known excessive past exposure to lead. Paired iliac crest, transiliac and tibial bone biopsies from these cadavers indicated that in bone biopsy specimens the lead/calcium ratio is more reproducible than the absolute lead concentration. There were no significant differences between the lead/cadmium ratio is more reproducible than the absolute lead concentration. There were no significant differences between the lead/cadmium ratios from the iliac crest, transiliac, or tibial specimens. Transiliac bone biopsies from 35 patients (13 patients showing symptoms of slight or moderate degree renal failure, medical history of gout and/or arterial hypertension and 22 lead workers with

chelatable lead in excess of 1000 micrograms) indicated that the lead and the lead/cadmium ratio in bone biopsies reflect the body lead stores as estimated by the EDT A test ($r=0.87$ and 0.83 , respectively). Chemical and histological studies of transiliac biopsies previously obtained from 153 dialysis patients (from 8 dialysis centers from Belgium, France, and Germany) for studies of aluminum-induced bone disease showed that chronic renal failure and dialysis do not cause accumulation of lead in bone and elevated bone lead does not appear to alter trabecular bone histomorphometry. We found that in 5% of the hemodialysis population studied, bone lead concentrations approximated levels found in active lead workers.

Wadeen RP.

Bone lead, hypertension and lead nephropathy.

Environmental Health Perspectives, 1988 Jun, 78: 57-60.

There is considerable clinical evidence that excessive lead absorption causes renal failure with hypertension and predisposes individuals to hypertension even in the absence of detectable renal failure. Recent analyses of transiliac bone biopsies indicate that unsuspected elevated bone leads may reflect the cause (or contributing cause) of end-stage renal disease in 5% of the European dialysis population. In these patients, bone lead levels were four times higher than in unexposed cadavers (6 micrograms/g wet weight) and approximated levels found in lead workers (30 micrograms/g). At present, the most reliable index of body lead burden is the CaNa_2EDTA lead mobilization test. In vivo tibial X-ray induced X-ray fluorescence (XRF) is a more practical noninvasive technique for assessing bone lead, which should find widespread application as a diagnostic tool and for epidemiologic studies.

Osterich JD.

* Body burdens of lead in hypertensive nephropathy.

Archives of Environmental Health, 1989 Sep-Oct, 44(5): 304-310.

Chronic lead exposure resulting in blood lead concentrations that exceed 1.93 mmol/l (40 micrograms/dl) or chelatable urinary lead excretion greater than 3.14 mmol (550 micrograms) per 72 hours has been associated with renal disease. A previous study had found greater chelatable urine lead with renal failure due to other causes, although mean blood lead concentrations averaged 0.92 mmol/l (19 micrograms/dl). To determine if chelatable urinary lead, blood lead, or the hematologic effect of lead (zinc

protoporphyrin) were greater in hypertensive nephropathy (when hypertension precedes elevation of serum creatinine) than in other forms of mild renal failure, we compared 10 study subjects with hypertensive nephropathy to 24 controls having a similar degree of renal dysfunction due to causes other than hypertension. Lead burdens were similar in both the study and control groups as assessed by 72 hour chelatable urinary lead excretion after intramuscular injection of calcium disodium EDTA (0.74 ± 0.63 vs 0.61 ± 0.40 μmol per 72 hours, respectively), and by blood lead (0.35 ± 0.23 vs 0.35 ± 0.20 $\mu\text{mol/l}$). We conclude that subjects from a general population with hypertensive nephropathy do not have greater body burdens of lead than renal failure controls.

Koster J; et al.

Mobilizable lead in patients with chronic renal failure.

European Journal of Clinical Investigation, 1989 Apr, 19(2): 228-233.

Blood lead (Pb) and urinary Pb before and after i.v. infusion of 1 g of Na_2Ca EDTA were determined (atomic absorption) in 16 control subjects and 91 patients with various stages of renal failure (median serum creatinine 2.5 mg dl^{-1}). Under baseline conditions, patients with renal failure had higher blood Pb levels (112 ng ml^{-1} , range 44-272 vs 76; 36-187 in controls: P less than 0.001) and lower urinary Pb ($16.2 \text{ nmol } 24 \text{ h}^{-1}$ 1.73 m^{-2} , $4.86-65.8$ vs. 33: 11-91 in controls: $P=0.001$). The increment in urinary Pb after EDTA infusion (mobilizable Pb) was higher ($795 \text{ nmol } 4 \text{ days}^{-1}$ 1.73 m^{-2} , range 155-5611 vs. 307; 131-1587 in controls; $P=0.001$). In 12 patients with renal failure (13%) mobilizable Pb was above the highest value in controls. Mobilizable urinary Pb correlated ($r=0.68$) significantly ($P=0.001$) with blood Pb, but only marginally with serum creatinine ($r=0.32$; P less than 0.007). Mobilizable Pb was higher in patients with renal failure and a history of smoking or occupational Pb exposure and tended to be higher in patients with alcoholism. Ten of 91 patients had gout; increased mobilizable Pb was present in three of the ten. The data confirm relatively high prevalence of elevated body Pb burden in European patients with chronic renal failure. The question is unresolved whether Pb plays a role in the progression of renal failure.

Goyer RA.

Mechanisms of lead and cadmium nephrotoxicity.

Toxicology Letters, 1989 Mar, 45(1-3): 153-162.

Exposure to lead results in accumulation in proximal renal tubular lining cells in the form of morphologically discernable inclusion bodies which are lead protein complexes. Acute nephrotoxicity consists of proximal tubular dysfunction and can be reversed by treatment with chelating agents. Chronic lead nephrotoxicity consists of interstitial fibrosis and progressive nephron loss, azotoemia and renal failure. Potential complications of lead neuropathy include gout and hypertension. Cadmium accumulates in renal tubular lining cells bound to metallothionein, a small protein containing 30% cystine. Metallothionein protects against nephrotoxicity by binding cadmium in a nontoxic form. Renal tubular dysfunction and chronic interstitial fibrosis occur when cadmium levels in the renal cortex exceed the critical concentration of about 200 micrograms/g. Recommendations are made for specific research needs.

Verscho M.

* Influence of occupational low-level lead exposure on renal parameters.

American Journal of Industrial Medicine, 1987, 12(4): 341-351.

↑ NAG

NAG
The influence of lead exposure on renal function was examined. In 155 lead workers and 126 control workers, lead in blood (PbB) and zinc protoporphyrin in blood (ZPP) were measured as indicators of exposure to lead; various proteins in urine were measured as parameters of renal functions. Regression and matched-pair analyses suggest that tubular parameters may be more influenced by lead exposure than glomerular parameters. Changes in renal function parameters may already occur at PbB levels below 3 $\mu\text{mol/liter}$ (600 micrograms/liter). The excretion of N-acetyl-beta-D-glucosaminidase appears to be the most consistent and sensitive parameter of any early effect on the tubular function.

E. REPRODUCTION

Decreased fertility in women, increased abortion and neonatal morbidity have been reported in the past but such effects are seldom encountered under the type of exposures which occur in industry today. There is, however, concern about potential risks to the fetus, particularly effects on the immature nervous system, since lead crosses the placenta readily.

Lead is considered as both an embryo and a fetal toxic substance. Considerable effort should be spent in limiting exposure of both the male and female prior to conception. Lead affects the sperm more readily than the ovum. The relevance of sperm morphology is that abnormal sperm can be produced by lead and the elevation in numbers of sperm abnormalities may be transmitted to subsequent generations. Sperm can be adversely affected during any cycle of sperm maturation.

The Occupational Safety and Health Administration (OSHA) has addressed the issue of reproductive toxicity in lead standard, 29CFR 1910.1025, Appendix C, published November 14, 1978. A copy of this is included in the handout. In summary, it indicates that exposure to lead can have serious effects on reproductive functions in both males and females, that women exposed may experience menstrual disturbances, that germ cells can be effected by lead and cause genetic damage in both eggs and sperm before conception, that infants of mothers with lead poisoning are at risk, that lead can pass through the placental barrier. They recommend a 30 ug/100g maximum permissible blood lead value in both males and females that wish to bear children.

1. Teratogenesis. Animal experiments clearly identify lead as a teratogen.

A teratogenetic assessment in humans was made by means of the status of the neonate following interuterine exposure to low levels of lead. By means of regression analysis it was decided that the Apagar scores, birth weight, length, head circumference, neonatal abnormalities and seven behavior scales were unrelated to either maternal or cord Pb-B. However, one "soft" sign of behavior was positive.

Like other chemicals, the nature of the lead-induced changes in the developing fetus are related to the time of gestation. For clarification, refer to the following figure.

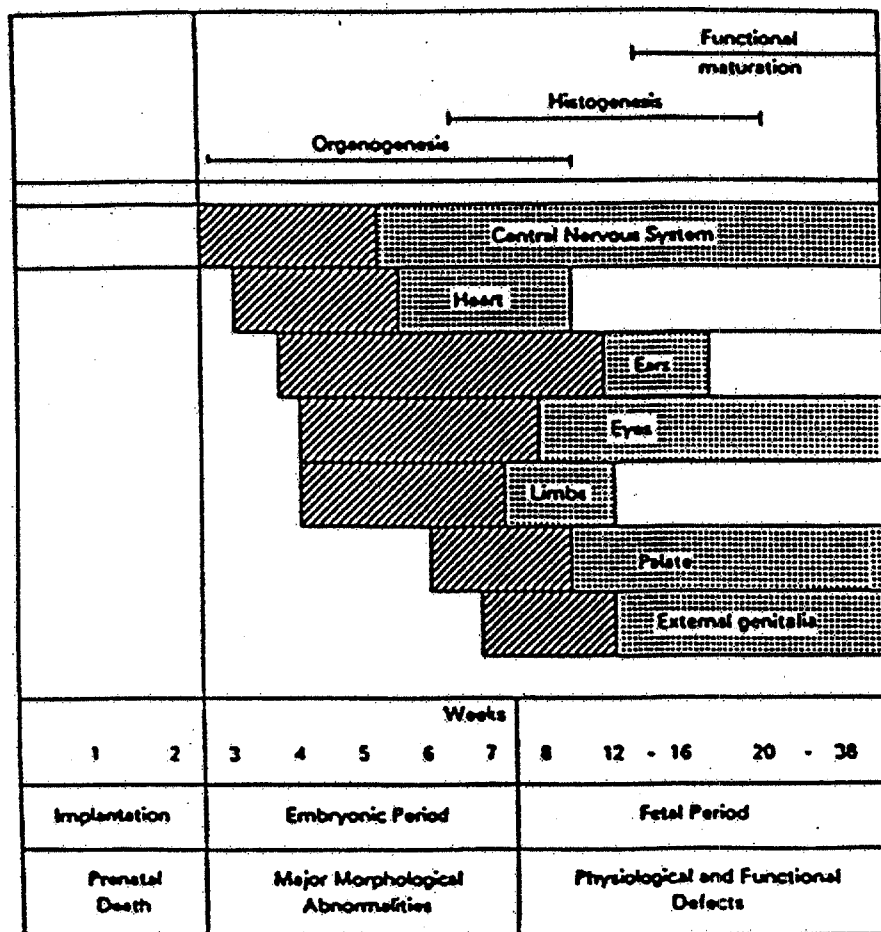


FIGURE 6.19.
Sequence of events in human development showing sensitive periods for developmental defects. Dark areas, most sensitive times; lighter areas, less sensitive times.

IV E

Assennato G; et al.

Sperm count suppression without endocrine dysfunction in lead-exposed men.

Archives of Environmental Health, 1987 Mar-Apr, 42(2): 124-127.

NUZM 10-120 x10⁶

To determine if increased lead absorption was associated with sperm count suppression or perturbation of the hypothalamopituitary system, we compared battery workers (N = 18), who were exposed to high airborne lead levels, with cement workers (N = 18), who were exposed to ambient lead levels. Blood lead, urinary lead, semen lead, and zinc protoporphyrin concentrations were markedly elevated (p less than .001) in battery workers. Battery workers had a significantly shifted (p less than .025) frequency distribution of sperm count (median count, 15 vs. 73 x 10⁶ cells/cc, respectively). There were no significant differences between the two groups in mean follicle-stimulating hormone, testosterone, prolactin, lutenizing hormone, or total neutral 17-ketosteroid levels. Potential confounding factors (alcohol, cigarette, and coffee consumption, frequency of intercourse, and days of abstinence prior to semen donation) were not significantly different between the two groups. These results suggest a direct toxic effect of increased lead absorption on sperm production or transport in man.

Paul M; Himmelstein J.

Reproductive hazards in the workplace: what the practitioner needs to know about chemical exposures.

Obstetrics and Gynecology, 1988 Jun, (6 Pt 1): 921-938.

A growing body of scientific evidence implicates occupational chemical exposures in the etiology of human adverse reproductive outcomes. Most reproductive toxins that have been investigated in sufficient detail have been shown to exert multiple effects on and through both men and women. In the face of growing public awareness, it is essential that clinicians develop a knowledgeable and effective approach to patient concerns about reproductive hazards in the workplace. Of vital importance is the accurate characterization of exposure at the worksite. Intervention strategies for worrisome situations include amelioration of worksite exposure or, as a last resort, temporary, compensated job modification or transfer. The clinician can obtain assistance in addressing the problem from several resources, including local regulatory agencies and occupational health clinics. Widespread involvement of knowledgeable health professionals can have a dramatic impact on improving this important contemporary public health problem.

CHRONOLOGICAL SCHEME OF POSSIBLE SITES FOR POTENTIAL
ADVERSE EFFECTS OF TOXIC AGENTS ON REPRODUCTION OR ON
THE ABILITY TO HAVE NORMAL HEALTHY CHILDREN

EFFECT PRIOR TO CONCEPTION

Endocrine effects, i.e.,
menstrual cycle, ovulation

Infertility (?mechanism)

AT CONCEPTION

Infertility- ?effect on sperm
Impaired implantation

DURING PREGNANCY

Spontaneous abortion

Stillbirth

Prematurity

Premature rupture of membranes

Teratogenesis

NEWBORN

Low-birth weight -- SGA

Problems of prematurity

Congenital anomalies

Increased perinatal morbidity/mortality

F. NERVOUS SYSTEM EFFECTS

1. Central Nervous System

Lead effects all parts of the nervous system. These range from subtle effects on performance all the way to severe encephalopathy.

Behavioral and psychological effects of long-term low lead exposure have been studied by many groups who have mainly attempted to delineate the border between safe and hazardous levels. In most of these studies the incidence of subjective

central nervous system symptoms has been found to correlate with the degree of lead exposure. The effects observed are:

- a) Slowness of performance.
- b) Psychomotor disturbances.
- c) Slight defects of intelligence.
- d) Changes in personality.

Table 1 Summary of results of earlier cross sectional studies of behavioural effects of occupational lead exposure

Study	Behavioural parameter			
	Verbal ability	Memory	Visuomotor function	Mood
Grandjean et al ^a				—
Hanninen et al ^b	0			—
Repto et al ^c	—	—	—	—
Valciukas et al ^d	0	—		—
Hogstedt et al ^e	0	—		
Baker et al ^f				

0 No effect. || Impaired. | Slightly impaired. — Not evaluated.

The psychomotor disturbances were detected by various behavioral, visual and verbal tests. Intellectual capacities were determined by various cognitive tests. Emotional alterations were determined by a symptom questionnaire. Depression, hostility, irritability, sleep disturbances, mood disturbances, restlessness, anxiety, impaired memory and personality changes were found. A significant correlation was found between these effects and the blood lead level as well as zinc protoporphyrin level. Zinc protoporphyrin was a better indicator of lead induced CNS effects than blood lead in some studies.

It is not yet possible to draw any definite conclusions about localization of the site of damage by lead in the brain, but it appears that long-term occupational lead exposure does give rise to neurobehavioral abnormalities, even with normal blood lead levels. Therefore, surveillance should be recommended in this area to prevent irreversible neurotoxicity from lead.

Acute encephalopathy may result from lead at doses greater than those encountered in industry today. Cerebral swelling, secondary to vascular injury is seen and there may also be direct damage to cerebral or cerebellar cells. At less intense exposure, symptoms will occur including headache, insomnia, bad dreams, personality changes and hyper-irritability. When fatal, brain lead concentrations may be relatively low compared to other organs, which suggests an increased sensitivity of the central nervous system. Permanent residual damage may occur secondary to convulsions in children. However, in the absence of convulsions or coma recovery should be complete. The CNS syndrome is frequently seen in children, but extremely uncommon in adults.

IV F 1

Needleman HL; et al.

- ★ The long-term effects of exposure to low doses of lead in childhood. An 11-year follow-up report. New England Journal of Medicine, 1990 Jan 11, 322(2): 83-88.

To determine whether the effects of low-level lead exposure persist, we reexamined 132 of 270 young adults who had initially been studied as primary school-children in 1975 through 1978. In the earlier study, neurobehavioral functioning was found to be inversely related to dentin lead levels. As compared with those we restudied, the other 138 subjects had had somewhat higher lead levels on earlier analysis, as well as significantly lower 10 scores and poorer teachers' ratings of classroom behavior. When the 132 subjects were reexamined in 1988, impairment in neurobehavioral function was still found to be related to the lead content of teeth shed at the ages of six and seven. The young people with dentin lead levels greater than 20 ppm had a markedly higher risk of dropping out of high school (adjusted odd ratio, 7.1:95 percent confidence interval, 1.4-10.7) and of having reading a reading disability (odds ratio, 5.8; 95 percent confidence interval, 1.7 to 19.7) as compared with those with dentin lead levels less than 10 ppm. Higher lead levels in childhood were also significantly associated with lower class standing in high school, increased absenteeism, lower vocabulary and grammatical-reasoning scores, poorer hand-eye coordination, longer reaction times, and slower finger tapping. No significant associations were found with the results of 10 other tests of neurobehavioral functioning. Lead levels were inversely related to self-reports of minor delinquent activity. We conclude that exposure to lead in childhood is associated with deficits in central nervous system functioning that persist into young adulthood.

★ Ong CN; et al.

- Neurological effect of lead exposure: a study of catecholamine metabolism. American Journal of Industrial Medicine, 1989, 16(6): 667-673.

In an attempt to examine the neurochemical changes of lead exposure, a study was conducted on 106 lead workers and a control group of 25 nonexposed workers. The urinary excretion of major catecholamine metabolites, homovanillic acid (HVA), and vanillylmandelic acid (VMA) were measured. Workers exposed to lead had a mean blood lead concentration of 43.2 micrograms/100 ml, whereas the concentration for workers not exposed to lead was 12.7 micrograms/100 ml. Urinary HVA was significantly elevated in the exposed group

when compared with controls (p less than 0.01). HVA was also found to be associated with an increase of lead in blood. Although not statistically significant, the VMA excretion was also noted to be moderately elevated; however, it is recognized that the present study was unable to establish a highly significant dose-response relationship between lead exposure and HVA excretion, as has been reported earlier in lead-poisoned children.

Pasternak G; et al.

* Cross-sectional neurotoxicity study of lead-exposed cohort.
Journal of Toxicology. Clinical Toxicology, 1988, 27(1-2): 37-51.

Although the toxic effects of lead have been known for centuries, lead intoxication is still widespread in the United States. Without baseline tests of neuropsychological, neurobehavioral and neurophysiological testing it may be difficult to detect subtle changes in neurological function after lead exposure. This may be further confounded by partial chelation treatment and exposure to neurotoxic mixtures or inability to quantitate alcohol consumption. We undertook a cross-sectional study to address these problems in 24 exposed and 29 control subjects in a plant that manufactured electrical components using fritted leaded glass to coat capacitors and transistors. Potentially exposed workers had blood lead levels ranging between 3 micrograms/dL to 135 micrograms/dL. Industrial hygiene monitoring revealed the plant's air lead levels ranged from 61 micrograms/m³ to 1,700 micrograms/m³ in excess of OSHA permissible exposure limits of 10 micrograms/m³/10 hour day. Using a specially designed battery of neurophysiological, neurobehavioral and neuropsychological screening tests, we demonstrated a significant difference from controls in measures of psychomotor speed, motor strength and verbal memory. Although limited by the cross sectional design, these findings support the hypothesis that the battery of neurophysiological, neuropsychological and neurobehavioral tests can detect a significant inter-group differences between lead-exposed and control subjects.

SEVERAL GOOD STUDIES - effect on mood

Langauer-Lewocika H; et al.

[Late sequelae of recurrent occupational lead poisoning--the status of the nervous system].

Language: Polish

Neurologia i Neurochirurgia Polska, 1987 May-Jun, 21(3): 212-216.

In 44 men with a history of repeated occupational lead

poisoning multidisciplinary clinical and laboratory investigations were carried out. The number of lead poisoning episodes was from 2 to 7. Apart from peripheral hypalgesia on the extremities (in 6 cases) no other neurological abnormalities were found. The motor nerve conduction velocity in the median, ulnar, radial, peroneal and tibial nerves was slightly slower in 27 cases and considerably slower in one case. Slowed down conduction velocity was most often observed in 2 nerves (12 cases) and in one nerve (9 cases), less frequently in three (4 cases) and four (2 cases) nerves. In one case this slowing down was found in all five studied nerves. Conduction changes were found in 21 peroneal nerves, 15 ulnar nerves, 12 median nerves, 7 tibial nerves and 2 radial nerves. The authors think that for the evaluation of the condition of the peripheral neuron in cases of past lead poisoning it would be sufficient to determine the conduction velocity in the ulnar and peroneal nerves. Plumbism neuropathy have the character of subclinical lesions not impairing motor skill.

Parkinson DK; et al.

✱ A psychiatric epidemiologic study of occupational lead exposure.

American Journal of Epidemiology, 1986, Feb, 123(2): 261-269.

The association of occupational lead exposure with neurophysiologic functioning was evaluated using data collected in 1982 in eastern Pennsylvania from 288 lead-exposed workers and 181 nonexposed subjects. Both current and cumulative exposure indices were used. After controlling for age, education, and income, few meaningful differences between exposed and control workers were found on either neurophysiological or psychosocial variables. Dose-response analyses indicated that among lead-exposed workers, cumulative current exposure were unrelated to neuropsychologic performance. The only meaningful associations occurred between exposure and level of conflict in interpersonal relationships. The results thus give evidence against hypotheses suggesting adverse neuropsychologic effects.

Stollery BT; et al.

✱ Cognitive functioning in lead workers.

British Journal of Industrial Medicine, 1988 Oct, 16(10): 698-707.

In a cross sectional study of occupational exposure to inorganic lead 91 men performed a series of microcomputer based tasks assessing sensor motor reaction time, memory,

attention, verbal reasoning, and spatial processing. Performance on the tasks was studied in relation to three ranges of blood lead concentration (low, less than 20 micrograms/dl; medium, 21-40 micrograms/dl; and high, 41-80 micrograms/dl) and exposure response correlations for blood lead concentration, zinc protoporphyrin (ZPP) (range 7-210 micrograms/dl), and urinary aminolaevulinic acid (ALA) (range 0.5-22.0 mg/l). The results show that the high group were impaired on most of the tasks used and, in general, the magnitude of the impairment correlated better with blood lead concentration than ZPP or urinary ALA. An examination of the patterns of task impairment indicated a general slowing of sensory motor reaction time which was relatively independent of the nature of the cognitive functions being tested. There was some evidence, however, suggesting mild impairment of attention, verbal memory, and linguistic processing. In general, workers with high blood lead concentrations showed clear impairment of sensory motor functions in the absence of correspondingly strong evidence for impaired processing and memory functions. It is argued that a general slowness in responding may underlie many previous reports of widespread cognitive impairment in lead workers.

Yokoyama K; et al.

- ✧ Reversibility of psychological performance in subclinical lead absorption.
Neurotoxicology, 1988 Fall, 9(3): 405-410.

To evaluate the reversibility of the effect of lead on psychological performance, five performance scale subtests of the Wechsler Adult Intelligence Scale were conducted twice at two-year intervals on 17 gun-metal foundry workers who had initial blood lead (BPb) concentrations of 30-64 (median 40) micrograms/dl. The results indicated that psychological performance was significantly affected by lead absorption in the first examination, resulting in a reduction in score on picture completion at the BPb level of 40-61 micrograms/dl. In the second examination, following a decrease in the BPb level, the reduced performance recovered. The two-year alteration in the picture completion subtest in all workers was significantly correlated with the corresponding change in mobilization yield of lead in urine by CaEDTA. It is suggested that the effect of lead on psychological performance is reversible at the BPb level below 65 micrograms/dl.

↑ 55 µg/DL = NOEL

Kumar S; et al.

Encephalopathy due to inorganic lead exposure in an adult.

Japanese Journal of Medicine, 1987 May, 26(2): 253-254.

A 30 year old male presented with acute gastrointestinal symptoms and encephalopathy. History, investigations and the response to chelator therapy led to the diagnosis of lead poisoning. Encephalopathy in an adult resulting from industrial exposure to inorganic lead are the main features of the case.

The entity of chronic lead encephalopathy in children is not well defined and it is difficult to separate recent events resulting from continued exposure from residuals of past exposure.

There is evidence that the concentration of lead in the blood resulting in chronic encephalopathy is lower in children (about 80 ug/dl) than in adults (above 120 ug/dl). There is also evidence that a sustained blood lead concentration of 50-60 ug/dl in early childhood carries a significant risk of subtle neuro-behavioral impairment. Some recent studies report a relatively low-level exposure influencing neuro-psychological disturbances.

A classification of central nervous system effects produced by chemicals containing lead as suggested by WHO include:

<u>Severity of Condition</u>	<u>Diagnosis</u>
Minimal	Organic affective reaction
Moderate	Mild chronic toxic encephalopathy
Severe	Severe chronic toxic encephalopathy

Mental Disorders Possibly Associated with Lead-induced Cerebral Dysfunction

Affect:	Shallow, exaggerated responses
Attention:	Reduced span, distractability
Cognitive Function:	Poor comprehension, decreased ability to abstract and perform arithmetic.
Judgment:	Impaired
Memory:	Decreased, recent more than remote.
Orientation:	Time and space > self

2. Peripheral Nervous System

Motor effects especially involving upper extremity extensor muscles without sensory involvement, constitute the most

V F 2

He FS; et al.

An electroneurographic assessment of subclinical lead neurotoxicity.

International Archives of Occupational and Environmental Health, 1988, 61(1-2): 141-146.

While heavy exposure to inorganic lead is capable of inducing symptomatic neuropathy in man, the subclinical neuropathy due to low levels of occupational lead exposure remains to be proved. The reported results of electroneurographic studies on lead workers, however, have been controversial. In this study, 40 lead smeltery workers and 50 non-exposed referents were investigated. The air concentrations of lead at worksites were 0.25 to 42.5 mg/m³. The geometric means of PbB, PbU and delta-Alau in lead exposed group were 10.03 micrograms/dl, 71 micrograms/l and 1.68 mg/l respectively, which were significantly higher (P less than 0.001) than those (7.01 micrograms/dl, 6.0 micrograms/l and 1.81 mg/l respectively) in the reference group. There were no clinical symptoms or signs of nerve damage in either group. Alcoholism and diabetes were excluded in both groups. Nerve conduction velocity was measured by a DISA 1500 electromyograph in both groups. Eleven electroneurographic parameters, including motor nerve conduction velocity (MCV) and distal latency (DML) of median, ulnar and peroneal nerves as well as sensory nerve conduction velocity (SCV) and distal latency (DSL) of median, ulnar and sural nerves, showed statistically significant differences between the two groups. However, the results of electroneurographic measurements of each individual in the lead-exposed group were all within the normal range. There was no correlation between the blood-lead levels and the neurophysiological measurements except for the median MCV. No correlation was seen between the median MCV and the exposure duration. (Abstract truncated at 250 words)

Ehle, AL. ← REVIEW

Lead neuropathy and electrophysiological studies in low level lead exposure: a critical review.
Neurotoxicology, 1986 Fall, 7(3): 203-216.

The literature on nerve conduction velocity (NCV) studies and electromyography in lead exposed populations was reviewed. All studies revealed some degree of defect in their experimental design. Disregarding these limitations, a consensus of the the studies indicates that a mild slowing (7%) of motor and sensory NCV may be present in the median and posterior tibial nerves, but that ulnar and peroneal NCVs are not slowed in subjects with blood lead levels of less than 60 micrograms/dl. No clinical correlations to this mild

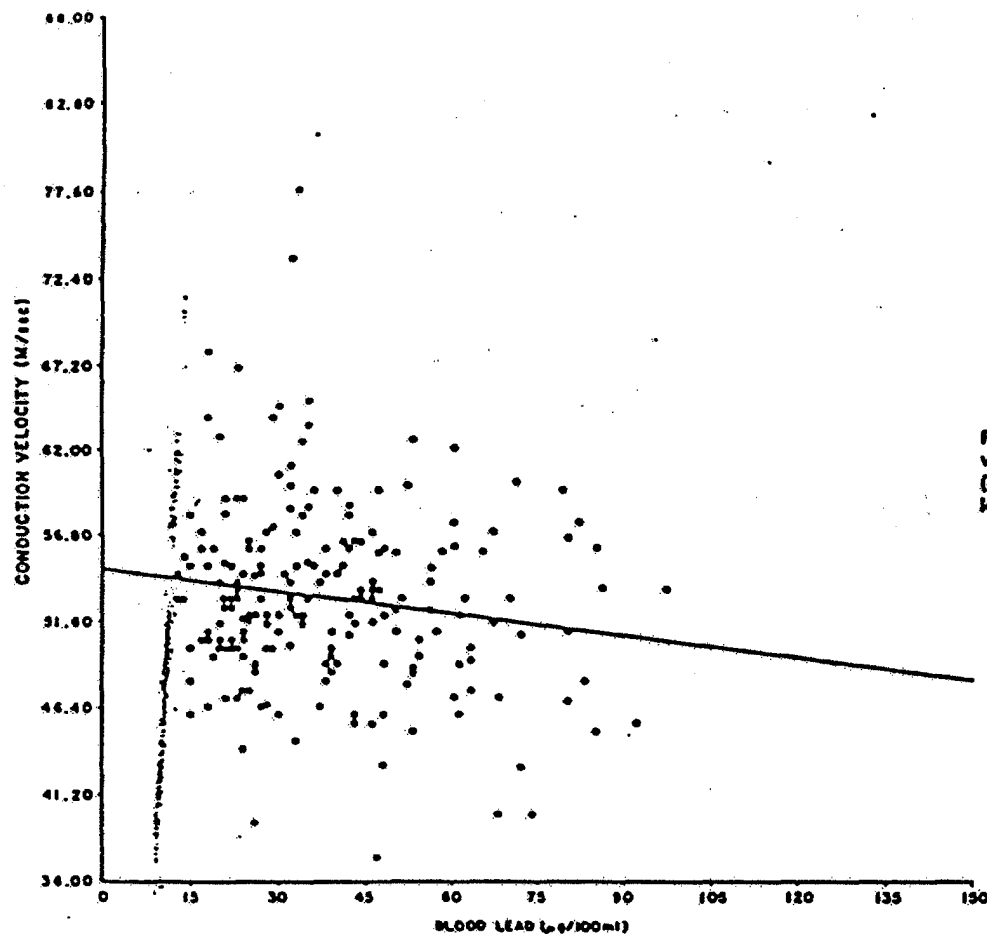
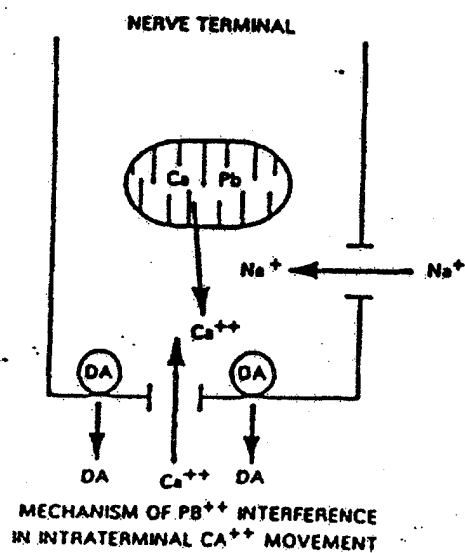


FIG. 5. Peroneal nerve conduction velocity vs blood lead level, Idaho, 1974. y (conduction velocity) = $54.8 - 0.45 \times$ (blood lead) ($r = -0.38$) ($n = 202$).

Possible mechanism of lead in influencing nerve conduction and neuronal response.



common aspect of the peripheral nervous system syndrome. Wrist-drop also occurs; the condition is, however, encountered much less frequently now than in the past and probably occurs only following prolonged massive exposure. Frank palsy may result in residual damage while milder cases may show complete recovery. It is believed that lead produces peripheral effects by causing segmental demyelination of peripheral nerves; there may also be involvement of the spinal cord and anterior horn cells. Nerve conduction velocity can be affected in the absence of clinical signs or symptoms, but there is no evidence that such changes are progressive or lead to functional impairment.

Reports of significant peripheral neuropathy are rare today. In the past, lead neuropathy was observed in persons with severe exposure. When it does occur, it is characterized by involvement principally of motor neurons with little sensory involvement. Changes in nerve conduction velocity can occur in persons exposed to lead without clinical evidence of nerve damage. A study of such a work population found that maximum motor nerve conduction velocities (MMCV) are significantly lower than expected. Nerves tested usually include the ulnar, median, radial and peroneal. The conduction velocity of the slower fibers (SFCV) are often reduced only in the peroneal nerve. Progressive slowing of nerve conduction is not associated with increasing exposure to lead as measured by the blood-lead concentrations or with commonly measured bio-chemical changes such as concentrations of FEP, urinary lead or reduced hemoglobin.

Electromyographic changes are inconsistent. A biopsy of peripheral nerve generally shows a loss of large fiber (greater than 7um in diameter).

A number of electrophysiologic methods are available for assessing possible effects of lead on the nervous system. These include.

- Maximal conduction velocity
- Sensory conduction velocity
- Conduction velocity of slower fibers
- Time of chronaxie
- Electromyography
- Amplitude of nerve action potential
- Variation of R-R interval
- Electroencephalography

J-8696

PRIMER COURSE FOR PHYSICIANS AND
ALLIED HEALTH PROFESSIONALS
IN THE LEAD INDUSTRY

Thursday, 20 September 1990

Charles Hine, M.D., Ph.D.
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I. TOXICOLOGY

TOXICOLOGY: The science regarding substances producing a noxious or untoward effect on the body, their identity, mechanism of action, diagnosis and treatment of the intoxication they produce.

1. SOURCES OF KNOWLEDGE IN HEALTH SCIENCE:

Scientific study of animals

Groups at work

Case evaluation

Epidemiology

2. CAUSES OF INTOXICATION STATES:

OVERDOSE:

Accidental

Purposeful

Relative

Idiosyncratic response

Accumulation of toxic substance
or its metabolites in tissues

Hypersensitivity

3. TYPE

Acute

Subacute

Chronic

4. EXTENT OF CHANGES:

Acceptable

Non-acceptable

Reversible

Non-reversible

Transferable (mutagenic)

5. MECHANISM OF TOXIC ACTION:

Directly toxic

Indirectly toxic

Producing irritation

Causing hypersensitivity

Affecting the immune response

Accelerating natural disease

Aggravating natural disease

Affecting reproduction

Causing teratogenic changes

Causing mutations

Causing cancer

6. FACTORS INFLUENCING THE TOXICITY OF A COMPOUND:

Quantity

Presence of other substances

Physicial state

Length of exposure

Absorbability

Solubility in body fluid

7. INFORMATION GAINED THROUGH TOXICITY TESTING:

Nature of toxic effect

Tissue changes

Relative toxicity class

CLASSIFICATION OF TOXICITY BASED ON ANIMAL TESTS GIVING
APPROXIMATE LD-50 VALUES

<u>Toxicity Rating</u>	<u>Route of Administration</u>		
	<u>Oral^a</u>	<u>Respiratory^b</u>	<u>Dermal^c</u>
Super Toxic	<5	<1	<5
Extremely Toxic	5-50	1-10	5-43
Very Toxic	50-500	10-100	44-340
Moderately Toxic	500-5000	100-1000	350-2010
Slightly Toxic	5000-15000	1000-10000	2011-22590
Practically non-toxic	>15000	>10000	>22590

^asingle dose value in mg/kg

^bsingle four hour exposure value in ppm

^csingle twenty-four hour exposure of skin value in mg/kg

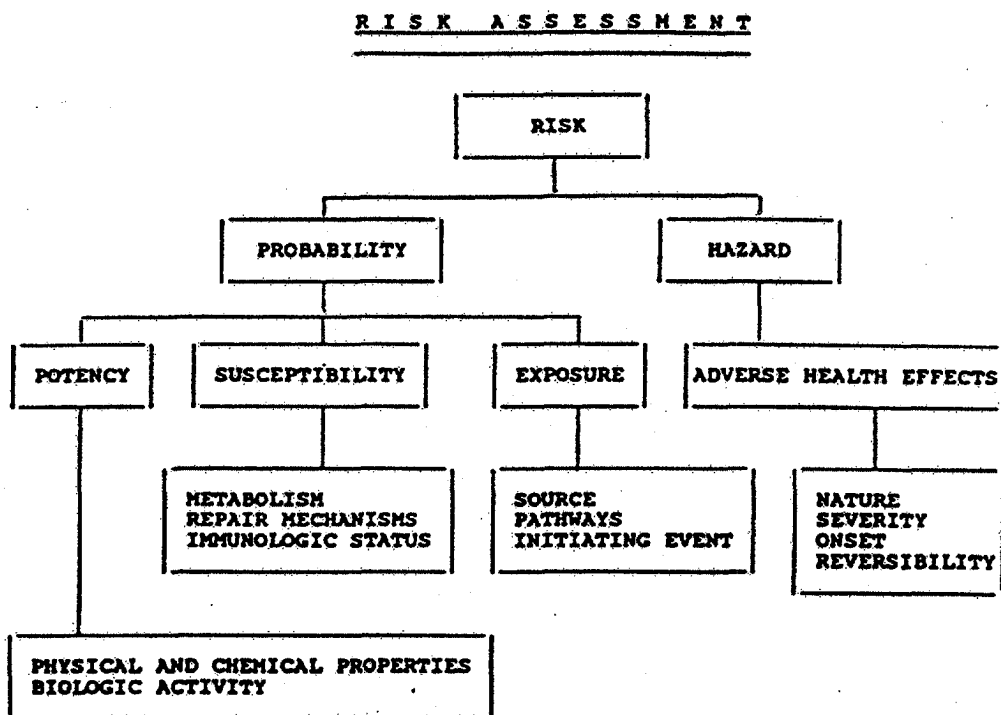
8. BASIC CONCEPTS IN ENVIRONMENTAL AND OCCUPATIONAL HEALTH

1. **TOXICITY:** The capacity of a chemical substance to produce injury.
2. **HAZARD:** The probability that injury or illness will result from a chemical under specified conditions.
3. **HAZARD IN THE WORK PLACE.** The probability is influenced by:

a) How the chemical is used	h) Pattern of air flow
b) Type of job operation	i) Housekeeping/main-
c) Work pattern	tenance operations
d) Operating temperature	j) Chemical properties
e) Exposed liquid surface	k) Education
f) Ventilation efficiency	l) Personal hygiene
g) Evaporation rate of chemical	m) Personal protection
4. **SAFETY:** The establishment of limits defined as the practical certainty that injury will not result from the use of the substance under specified conditions of quantity and manner of use.

5. **RISK:** The chance (probability) of injury, damage or loss.

A thing is "safe" if the risks are judged to be acceptable:



II. EXPOSURES

A. ENVIRONMENT

A number of studies have shown increased concentrations of lead in the hair, blood and urine of persons living near point sources. Factors influencing the concentration in the blood include: age, dust levels in the house, distance from the point source.

1. Air

Location is the principal determinant of the concentration. Non-urban air is less than 0.5 ug/M. residential areas in metropolitan cities less than 2 ug/M. Traffic areas may reach a maximum of 10 and means of 6.5 ug/M. In general, blood-lead levels increase with urbanization. It is difficult to establish any direct relationship between lead levels in the ambient air and lead levels in blood and urine.

Atmospheric lead emissions from human activity is estimated at about 450,000 tons per year, compared with 25,000 per year from natural sources.

2. Soil

Concentration of lead is usually 2-200 ppm, with mean values about 16 ppm. Road dust contains from 160-3,500 ppm and lead mining areas 20,000 ppm.

Soil lead content greater than 10,000 ppm may result in increased absorption in children who practice soil pica. Increase in soil lead of 1,000 ppm has given rise to increased lead count of locally grown vegetables. The increase in the blood is about 4.2 ug/dl.

3. Objects

Lead poisoning has been reported in infants given baby folk remedies, which are known to the parents to contain lead. Two Mexican remedies known as Azarcon and Greta contain high concentrations of lead, approximately 10 percent of Mexican-Hispanic families in the Los Angeles area have admitted prior use.

Other lead containing objects about the home have in the past included lead-nipple shields, toys, glazed bowls and lead used in stills.

B. HOME

1. Paint

Formerly, lead based paint in older homes was a source of exposure for children who practiced pica. The hobby of

working with leaded glass, which involves the use of leaden strips to outline pieces of colored glass and hold them in place, has given rise to lead intoxication from soldering the seams, in the absence of proper precautions and safety measures.

2. Dust

The most important sources for children in addition to lead-based paint, are lead-contaminated dirt and household dust. Children living in urban settings may have as much as 2400 ppm on their hands, when outdoor dirt contains 1200 ppm and indoor dust contains 11,000 ppm.

Comparison of Lead Concentrations in Household Dust with Children's Blood Lead Levels, Memphis, November, 1975.

DUST LEAD CONCENTRATION (PPM)	NO. OF CHILDREN	CHILDREN'S BLOOD LEAD LEVEL (UG/100 ML)
0-1000	18	21.8 ± 7.8*
1000-2000	5	41.6† ± 11.1
2000-3000	5	46.2† ± 21.1
3000-6000	4	65.0† ± 10.4
7000-80,000	6	73.3† ± 34.0

*Mean ± SD.

†Significantly > mean level of children exposed to 0-1000 ppm level of lead in dust (P < 0.001).

C. FOOD AND BEVERAGE

Lead concentrations in typical foods in the United States range from 0.1-0.5 ug/g. High concentration may occur on leafy vegetables in gardens due to air fallout. Pooled bulk milk contains about 40 ug/L. A processed milk will contain 200 ug/L. National Research Council estimates the usual intake from 100-200 ug/day from all foods.

There are two routes whereby the vegetation becomes contaminated from lead. The first is from soil sources via root uptake, the other from aerial deposition onto the plant leaves and stems. Lead ions absorbed in clay particles or organic matter are not in solution and therefore not freely available for plant uptake. The lead content is highest in crops with leafy tops and lowest in root crops. Increased alcohol intake but not smoking increases the blood lead level in persons not otherwise exposed to lead.

II B2

Schneitzer L; et al.

Lead poisoning in adults from renovation of an older home.

Annals of Emergency Medicine, 1990 Apr, 19(4): 415-420

Presented is the case of a group exposure to lead occurring during the removal of lead-based paint from an older home. One patient had symptoms from the time of exposure to the time of presentation, when he was acutely ill and encephalopathic. The patient was treated successfully with an initial course of British Anti-Lewisite agent and calcium disodium versenate (CaEDTA) chelation, and two subsequent chelations with CaE-DTA alone. The other two patients had elevated lead levels but were asymptomatic. They were followed closely, and their lead levels steadily declined over several months. The evaluation and treatment of lead poisoning and excessive lead levels in adults is discussed, as is the need for physicians and the lay public to become aware of the hazards of renovating older homes.

II E

Geier B; et al.

Annales de Gastroenterologic et D Hepatologic, 1988 Jun-Sep, 21(1): 193-195.

We report a case of lead poisoning resulting from the ingestions of solid metallic lead. A 24 year old patient was admitted for abdominal pain and microcytic anemia. Review of the literature suggests that clinical manifestations of chronic poisoning by solid lead in adults are extremely rare. Their misreading can lead to erroneous diagnosis.

Peglicua A; et al.

Lead poisoning: clinical, biochemical, and hematological aspects of a recent outbreak.

Journal of Clinical Pathology, 1990 Apr, 13(1): 277-281

The clinical, biochemical, and hematological aspects of a recent outbreak of lead poisoning, in which exposure was related to the oxyacetylene cutting of red lead painted ironwork, were investigated. Initial suspicion was raised when a blood film showed punctate basophilia which remains a simple and useful method of picking up lead toxicity. Estimations of blood lead concentration and conventional laboratory data confirmed the diagnosis. Although there was prominent punctate basophilia spectrophotometric analysis showed only negligible accumulation of pyrimidine-5'-nucleotides despite severe suppression of pyrimidine-5'-nucleotides activity. The pattern of the red cell glycolytic intermediates, investigated for the first time, suggested that lead may also affect glycolysis at the hexokinase step.

Once the diagnosis was made intravenous chelation treatment was begun with a rapid improvement in symptoms. Long term follow-up is required to assess any sequelae of intoxication. These cases emphasize the classic features of lead poisoning, and despite the currently available diagnostic tests, lead intoxication may still go unrecognized unless a thorough occupational history is taken.

II E

Lussenhop DH; et al.

Lead exposure and radiator repair work.

Am J Public Health, 1988 Nov, 78(11): 1558-1560.

In 1986, the ambient air for lead in radiator repair shops in the Minneapolis-St. Paul metropolitan area exceeded the Occupational Safety and Health Administration (OSHA) action level in nine of twelve shops sampled by Minnesota OSHA. We therefore sought to determine the prevalence of lead exposure/toxicity in this industry. Thirty-five radiator shops were identified, thirty were visited, and fifty-three workers were studied. The mean blood lead level was 1.53 (range 0.24-2.80). Seventeen individuals had blood lead levels greater than or equal to 1.93 $\mu\text{mol/L}$ (40 micrograms/dL). The mean zinc protoporphyrin level (ZPP) was 0.55 $\mu\text{mol/L}$ (range 0.16-1.43). No single worksite or personal characteristic was a strong determinant of either blood lead or ZPP level.

Matte TD; et al.

Lead exposure among lead-acid battery workers in Jamaica.

American Journal of Industrial Medicine, 1989, 16(2): 167-177.

To assess lead exposure in the Jamaican lead-acid battery industry, we surveyed three battery manufacturers (including 16 production workers) and 10 battery repair shops (including 23 battery repair workers). Engineering controls and respiratory protection were judged to be inadequate at battery manufacturers and battery repair shops. At manufacturers, 38 of 42 air samples for lead exceeded a work-shift time weighted average concentration of 0.050 mg/m^3 (range 0.030-5.3 mg/m^3), and nine samples exceeded 0.50 mg/m^3 . Only one of seven air samples at repair shops exceeded 0.050 mg/m^3 (range 0.003-0.066 mg/m^3). Repair shop workers, however, had higher blood lead levels than manufacturing workers (65% vs. 28% with blood lead levels above 50 micrograms/dL, respectively). Manufacturing workers had a higher prevalence of safe hygienic practices and a recent interval of minimal production had occurred at one of

the battery manufacturers. Workers with blood lead levels above 60 micrograms/dl tended to have higher prevalences of most symptoms of lead toxicity than did workers with lower blood lead levels, but this finding was not consistent or statistically significant. The relationship between zinc protoporphyrin concentrations and increasing blood lead concentrations was consistent with that described among workers in developed countries. The high risk of lead toxicity among Jamaican battery workers is consistent with studies of battery workers in other developing countries.

D. WATER

Rain water contains 34-300 ug/L. For many years the lead concentration in water supplies in the USA have not exceeded 50 ug/L, the U.S. Public Health Service standard. When lead pipes or tanks are used for storage, the concentration may be as high as 3,000 ug/L. A correlation was shown between lead concentrations in household water and renal insufficiency and hypertension in Scotland. Twenty percent of the people had abnormal renal functions as indicated by an increased BUN. None of the persons had signs or symptoms of lead intoxication and the mean of exposure was 21.5 years.

E. WORK**1. Chemical Forms of Lead**

Metallic

Inorganic (salts)

Organic

Lead is a metallic element, molecular weight 207.2. This heavy metal has a specific gravity of 11.35, melting point of 327.4° C and a boiling point of 1755°C. Its vapor pressure becomes significant, from a health standpoint, only above 500 C. Only a few lead compounds are appreciably soluble in water, but most are sufficiently soluble in body fluids to be toxic, especially when inhaled in finely divided form.

2. Uses**a. Metallic Lead and Alloys**

Batteries - oxides and grids
largest use - 80 percent recycled

Cable - protective covering

Construction - pipe, sheet

Manufacturing - reaction vessels, storage tanks

Shot, solder, radiation shielding - weights and ballast, tubes, brass and bronze bearings, type metal

b. Compounds**Uses**

Oxides

Pigments

Battery manufacturing

Anti-corrosive

Specific Compounds

Lead chromate	Road signs (chrom yellow)
Lead arsenate	Insecticides
Lead nitrate	Explosives
Tetraethyl lead	Anti-knock
Lead silicate	Glazes

c. Work with Increased Risk

High Risk	Welding, cutting-shipbreaking (oxyacetylene, 3500°C), sintering, smelting, refining, pasting, assembling, welding, storage, battery, brass, leaded steel, solder grinding.
Moderate Risk	Mining, soldering, cable makers, sheet lead, pipe, shot, glass blowing, pottery glaze makers.
Low Risk	Traffic, garage, service station, jewelers, pipe fitters.

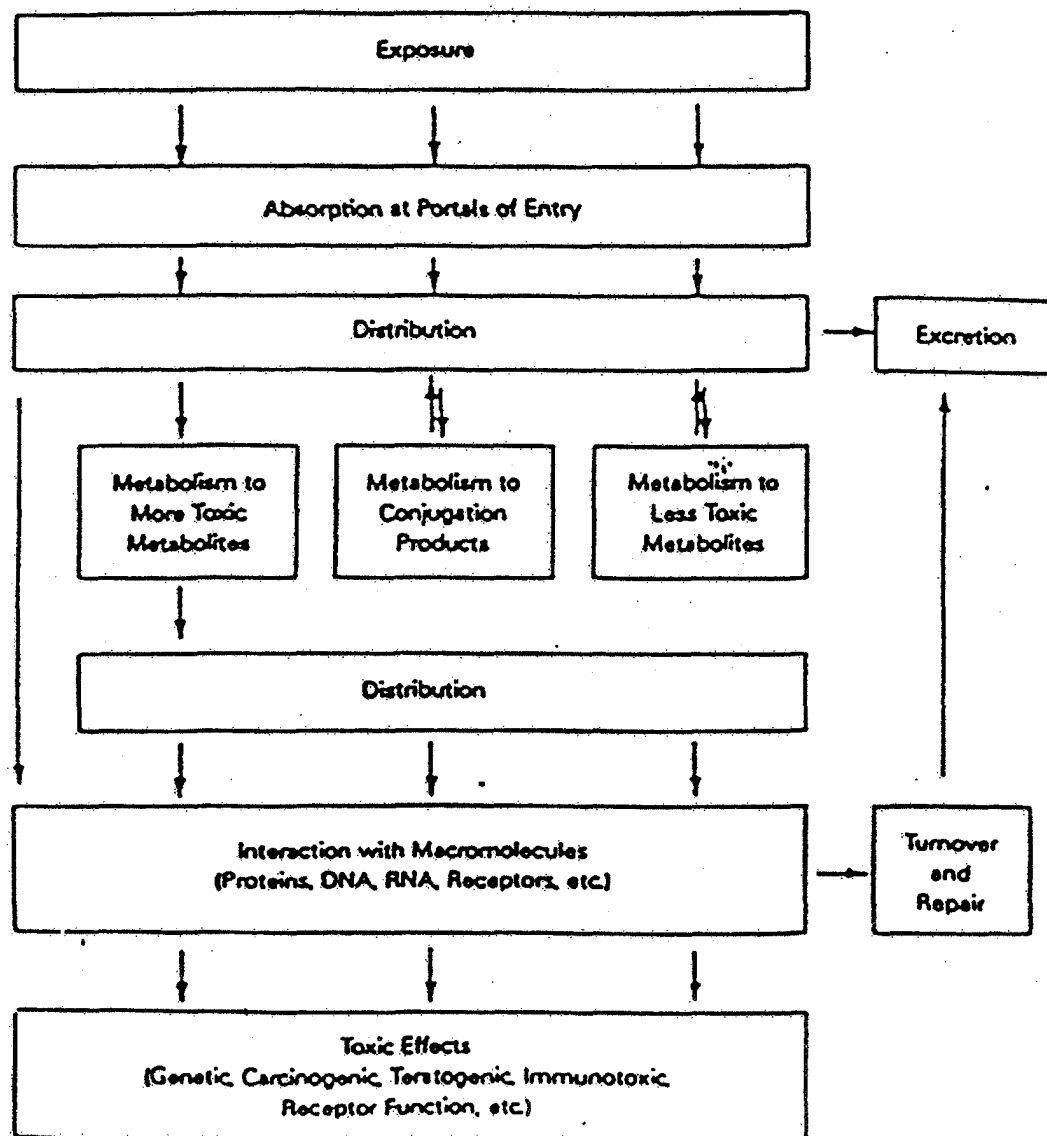
Children of parents who work in the lead trades have increased lead concentrations due to extraneous exposure.

III. TOXICOKINETICS

Lead is found in the tissues of all normal persons. The principal route of entry is by ingestion, but respiration also accounts for some of the body burden. Total body lead is relatively constant around the world except for those persons who have increased body burdens due to industrial or non-industrial lead exposure.

Sequence of events following exposure to exogenous chemicals

A diagram depicting the pathways that an absorbed chemical follows through the body, its excretion, deposition and the possible effects on the body are summarized below.



5. Absorption

The major dietary factors increasing the absorption of lead from the gut:

High Vitamin D
High Protein
High Fat
Low Calcium

Fasting
Low Mineral
Low Iron
Low Vitamin C

Additional factors increasing or decreasing lead absorption from the gut are listed in Appendix I.

Oral. Depending on various gastrointestinal and physiological factors such as acidity, solubility and motility, 5 to 10 percent of lead present in the G.I. tract is absorbed into the blood stream. Approximately 100 to 200 ug of lead are normally ingested daily by way of food and beverages. If daily intake is increased to about 450 ug, a slow accumulation of lead in bone and possibly other tissues may result, although blood lead may not be increased until oral intake reaches 1 mg/day. Reabsorption from the gut is complete after about two days.

Children absorb more lead than adults because of the increased calcium and relatively low content of zinc and iron in their diets.

Inhalation. Lead-contained particles in the ambient air have an aerodynamic diameter of approximately 0.1-10 microns, with a predicted deposition of the airways of 35 percent. Depending on the physical and chemical properties of the aerosol, this may range from 5 to 50 percent. Absorption of respired lead depends on particle size, density and solubility and also on mucociliary action, rate and depth of respiration and other factors. Sixty-five percent of inhaled lead is immediately exhaled; of the percent retained, 9 percent is cleared to the blood directly and 45 percent is cleared to the G.I. tract where 10 percent is absorbed. While its exact fate is not known for certain, the net absorption of inhaled lead is estimated to be about 15 percent. In industry, this presents a significant source and serves as the basis for establishing a threshold limit value time weighted for an 8-hour day. (Ingestion of lead from industrial exposure, while contributing to absorption, is not considered in determining the TLV.)

When the air concentration is expressed in ug/M^3 and the blood lead in ug/dl , the following relation exists. For each $1 \text{ ug}/\text{M}^3$ of lead the blood lead increases by $1.2 \text{ ug}/\text{dl}$ (0.6-3.2).

Skin Exposure. Inorganic lead is not absorbed directly through the skin and therefore skin exposure presents a hazard only when lead on the skin enters the body secondarily by way of ingestion.

Average daily intake. The daily intake of lead arises from three sources for the majority of the population. Not all the lead is absorbed, a positive balance does occur with time. The average person has about 100 mg in his body.

<u>Vehicle</u>	<u>Total Amount (ug)</u>	<u>Amount Absorbed (ug)</u>
Air	20	10
Water	20	20
Food	200	20
TOTAL	240	50

B. TRANSPORT

Lead is transported principally by binding to the red cell's hemoglobin and to a small extent in solution in the plasma; its diffusion into the tissues probably is regulated by the activity of the lead binding protein (LBP). It is characterized as having a molecular weight of 10,000 Dalton, and by being found only in lead-exposed persons. It has a protective role in the erythrocyte. Deficiency of the protein leads to clinical and biochemical manifestations of lead intoxication at low levels.

Chelation reduces lead bound to hemoglobin but increases the lead bound to the LBP. Diminished capacity to synthesize LBP may increase susceptibility to lead.

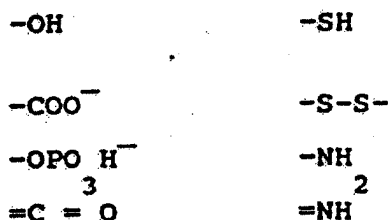
Ninety percent of lead in the blood is bound to the red blood cells.

C. DISTRIBUTION

Once absorbed, lead is transported to one of the three physiologically distinct compartments. One, a "rapid" exchange pool consisting of blood, tissue fluids and soft tissue; two, an intermediate exchange pool consisting of soft tissues and actively exchanging parts of the skeleton; and three; a "slow" exchange pool consisting primarily of bone. Immediately following absorption, about 50 percent of lead is found in three tissues: the kidney, liver and blood. Approximately 20 percent of the total lead absorbed is localized in the kidneys, which represents the highest concentration of lead in any organ in the earliest stages of acute lead intake. The half-life of renal lead is about two days. Pool one contains approximately 4 percent of the body burden of lead, where overall half-life is about 36 days. Compartment two, contains 2 percent of the lead body burden

with a half-life of about 40 days. Pool three contains about 94 percent of the body burden, with a half-life of 10,000 days.

Lead in the tissues binds with a number of chemical molecules. The principal ones are:



Studies of mobilizable lead in school children and adolescents, indicates that the mobile fraction of the body lead burden increases exponentially as the blood lead concentration increases arithmetically in the range of 10-75 ug/dl.

When in equilibrium, soft tissue concentrations of blood vary from 20 to 100 ug/100 grams. The greatest storage is in tissues containing increased calcium such as the bone and teeth and keratin as in the hair and nails. Typical tissue concentrations are:

Blood	20	Bone	1000
Muscle	50	Hair	300
Liver & Kidney	10	Teeth	500

The blood lead concentrations in a group of normal children and those of employees of fathers exposed at work are shown in the figure below.

