

Public Health Consequences of Heavy Metals in Dump Sites

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Metals differ from most synthetic organic chemicals in that their clinical manifestations are well known and methods for their measurement in the body are generally well established. Since metals are ubiquitous, special care should be taken to identify the source, whether dump site or not. Isotopic ratios may be used for lead. Time of exposure may be highly variable so estimates will be necessary of integrated "dose-commitment." Transmission to man will follow many pathways. The contamination of children's hands and clothing by dust may be an important route. Because effects are so different, the chemical species (e.g., organic versus inorganic forms) of each metal must be identified. Exposure assessment requires identification of suitable indicator media, usually blood in the case of lead, urine with cadmium and inorganic mercury, and blood or hair with regard to methylmercury. Human head hair may have considerable potential, as it may provide a recapitulation of past exposures. The first health complaints associated with most metals are usually nonspecific. The complex social, political, and legal issues strongly indicate the need for objective tests for health effects. Most important is the identification and measurement of the critical effect, i.e., an effect that alerts the public health authorities that further exposure should cease. For example, in the case of lead, the critical effect is hematologic; with cadmium it is the presence in urine of abnormally high concentration of small molecular weight protein; and with mercury no early objective test has yet been devised.

Introduction

Cadmium, lead and mercury are all toxic metals without any essential biological roles. Mercury and lead belong to what Hunter (1) calls the "ancient metals," a term reflecting human exposure to these metals for several thousand years. Their clinical effects, at least in overt cases of poisoning, are well known. Ramazzini's famous book (2) on the disease of occupations, first published in the 1700s, gives excellent clinical descriptions which could hardly be improved upon today. Even with cadmium, a relatively recent hazard, occupational exposures, incidental poisonings and the community exposures leading to Itai-Itai disease in Japan (3) have provided a clear picture of its clinical toxicity. This

history stands in contrast to many other substances described at this meeting; these are so new or circumscribed in distribution that little toxicological information about them is available.

A second advantage that investigators enjoy in evaluating human exposures to heavy metals is that techniques are now available to measure such metals in most indicator media and at sufficiently low concentrations that even levels in the nonexposed populations can be estimated. Some advanced techniques actually allow us to determine the source of the exposure by analysis of stable isotopes and biological indicator media. In addition, there is considerable experience, drawn mainly from occupational exposures or exposure of populations near heavy metal industries, to allow us to identify appropriate indicator media reflecting exposure to or body burden of the metal.

Given these advantages, it might seem that one has a relatively easy task in suggesting a means of assessing exposure and health effects in individuals living in or near dump sites containing heavy met-

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als. Heavy metal toxicology, however, depends not only upon our past experience with these metals but also upon developments in modern biology. Such developments can change both our test procedures and our criteria of toxic levels and enlarge the spectrum of biological effects suspected of association with exposure. This report will try to blend the old with the new.

In evaluating different assessment and analytical methods, we have also tried to consider the complex social, political and legal situations that arise at dump sites. Tests should be designed for objective values; that is, their data should be resistant to biases in the examiner, the examinee or the general scientific, medical and political milieu that surrounds such an investigation, as recommended by the Rall Committee (4). Although questionnaires and neurological and psychological testing, for example, may be very useful in a controlled study of a well-characterized population, they are of less utility in the situations existing at most dump sites. For this reason, we have concentrated on laboratory tests as far as possible in specifying how to assess human exposure and health effects of heavy metals. We also support the concept developed by the Subcommittee on Toxic Metals of the Permanent Commission and International Association of Occupational Health (5) which defined what is termed a "critical effect" of a metal; that is, a measurable effect which acts as an early warning sign such that, if appropriate preventive action is taken, further more serious and irreversible effects will be avoided. Our proposed laboratory tests are aimed at identification of the "critical effect." Questions for which such laboratory tests are not available will be stressed as important gaps in our current toxicological and clinical tools.

Sources of Exposure: Estimated Contributions

Toxic metals present some special problems because, even with dump sites and equivalent point sources, there remain other contributions. Fossil fuel combustion spews enormous quantities into the atmosphere because metals are indigenous constituents of the earth's crust. Geological processes may enhance the biological burden as in the case of mercury. Because of such wide distribution, there is an obvious problem in separating the contribution of the point source from food contributions, airborne contribution from remote sources, etc.

Consider the case of lead. Airborne dispersal of lead from automobile emissions raises annual mean concentrations above busy urban roads to within

the range of 2 to 6 $\mu\text{g Pb/m}^3$. The air levels fall rapidly with distance from the road; 50 m away, average air concentrations fall to about 20% of the roadside values (Fig. 1). As the distance increases, air lead from the road merges gradually with lead from all traffic sources, reaching typical urban levels of about 0.5 $\mu\text{g Pb/m}^3$. The air concentrations in rural areas are about 0.1 $\mu\text{g/m}^3$. Thus, "background" levels in the dump site area (both atmospheric and soil levels) will depend upon traffic patterns, urban versus rural location, and so forth.

One instance in which this has been attacked in an ingenious and technologically sophisticated manner arose from an attempt to identify the source of lead responsible for the death of a group of horses grazing in a pasture close both to a point source (a lead smelting plant) and an extended source (a super highway). Measurement of the natural abundance of three stable isotopes of lead, ^{207}Pb , ^{206}Pb and ^{204}Pb , revealed that lead originating from the smelter had low values for the ratios $^{206}\text{Pb}/^{204}\text{Pb}$ and $^{206}\text{Pb}/^{207}\text{Pb}$ compared to values obtained in samples of lead obtained at the roadside and remote from the smelter (Fig. 2). Samples from horse tissue fell between values from grass in the pasture and distant grass. It was concluded that the "horses which died of lead poisoning obtained approximately equal parts of smelter and gasoline lead" (7).

This technique, unfortunately, is available only

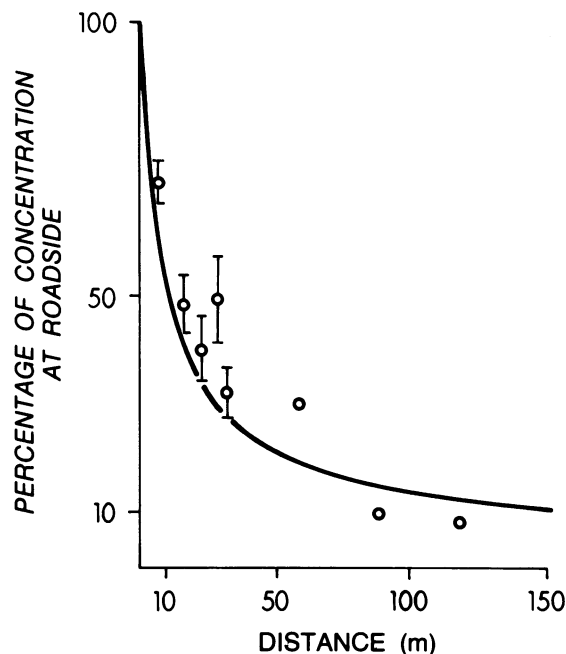


FIGURE 1. Concentration of airborne lead in relation to distance away from motor ways (6).

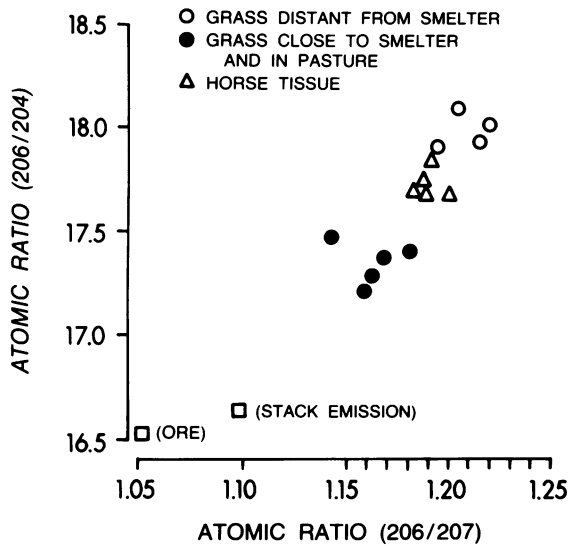


FIGURE 2. Isotopic composition of environmental samples of lead: (○) samples of grass and dirt collected near the road site; (●) samples of grass collected close to a lead smelter; (□) samples collected from the ore and the stack emissions from the smelter. Lead in horse tissue was found to have intermediates between roadside lead and smelter lead (7).

for metals that belong to a natural radioactive decay sequence. Alternatively, the identification and measurement of individual chemical species of the metal may be useful if the dump site contains synthetic compounds of the metal that differ from those occurring in the natural environment.

Dose Commitment

The concept of dose commitment originally was developed to deal with ionizing radiation; it was borrowed to provide a model for the environmental impact of pollutants, especially metals (8). Since dose has a limited meaning when discussing pollutants, the term "exposure commitment" was substituted. In this treatment of the problem, exposure is defined as the integral of the concentration over time in a specified reservoir; exposure during the time interval t_1 to t_2 is expressed as:

$$E_i(t_1, t_2) = \int_{t_1}^{t_2} C_i(t) dt$$

where $C_i(t)$ is the concentration of a pollutant in a reservoir i at time t . Expressing exposure in such a fashion is especially suitable for chemical waste disposal areas because the interval (t_1, t_2) is highly variable. The exposure commitment model has also been amplified to include transport through a

sequence of environmental reservoirs, a salient consideration for metals because of the way they move from compartment to compartment in the environment, sometimes undergoing significant chemical modification in the process. Mercury (8) and lead (9) have so far been subjected to such an analysis. Figure 3 diagrams the compartments and processes that participate in the transfer of lead to humans. Table 1 provides estimates of concentrations in various reservoirs.

Transmission to Man

Chemical waste sites complicate the exposure commitment model because they distort the topography assumed by the model, which averages over an area. They also multiply the sources and possible transformations. Contamination of aquifers supplying household water is a problem increasingly complicating environmental assessment because it expands the area of contamination. Freshwater sources may also suffer indirect as well as direct contamination, with possibly unforeseen consequences. Acid rain leaches metals from soil (9). It also enhances the uptake of methylmercury by fish—as in the Adirondack lakes (10). Chemical waste sites broaden the hazard because they themselves may be characterized by low pH values; corrosive acids have frequently been reported. In addition, high concentrations of toxic metals in such

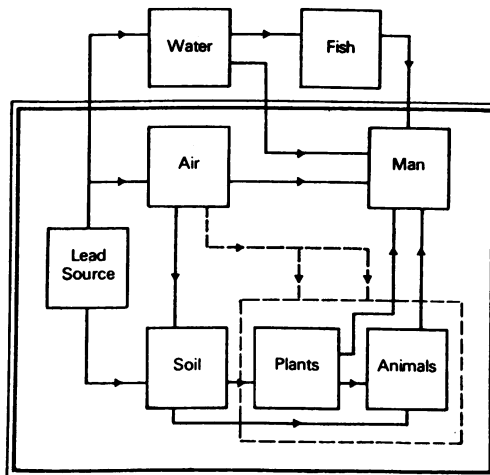


FIGURE 3. Diagrammatic representation of the compartment and processes that participate in the transfer of lead to humans. Plants and animals are effectively aggregated into one compartment, diet. Also direct input to animals and plants from the atmosphere are neglected (8).

Table 1. Summary of data for lead assessment example.^a

	Year	Value
Physical data		
Deposition velocity		0.5 cm/sec
Density of soil		1.4 g/cm ³
Air inhalation rate		22 m ³ /d
Adult human blood volume		5.2 L
Fractional deposition of particulates in lungs		0.35
Lead data		
World industrial rates production	1946	1.6 Mt/yr
	1970	4.0
Input to atmosphere		
	1933	0.002 Mt/yr
	1953	0.012
	1970	0.38
Atmosphere levels		
Non-urban sites near cities		200 ng/m ³
Rural areas		100 ng/m ³
Remote areas		20 ng/m ³
N. Atlantic		10 ng/m ³
N. Pacific and Indian Ocean		5 ng/m ³
Hydrosphere levels		
Rain water		34 µg/L
Rivers (USA)		7 µg/L
Tap water		4 µg/L
Ocean near shore (surface)		0.16 µg/L
Near shore (deep layers)		0.03 µg/L
Open ocean		0.06 µg/L
Lithosphere levels		
Soil (agricultural)		50 µg/g
Rocks		22 µg/g
Sediments freshwater		25 µg/g
Ocean (open)		148 µg/g
Ocean (near shore)		39 µg/g
Man		
Blood (rural residents)		12 µg/100 mL
Bone		3-9 µg/g
Parameter values		
Effective depth of Pb in soil		10 cm
Mean residence time of Pb in soil		300 yr
Mean residence time of Pb in blood		23 days
Dietary intake rate		40 mg/yr
Fractional absorption to blood from lungs		0.5
Fractional absorption to blood from GI tract		0.1

^aAdapted from Table 1 of O'Brien (8).

sites may be especially susceptible to acid rain because they are not bound to soil or rock.

Transport into residences may also be enhanced. Leakage into basements was noted at the Love Canal area and elsewhere. Entrainment into the home is another potential source of exposure. Lead industry workers, such as those in battery plants, may bring lead dust into the home via work clothes and expose their families to high ambient levels. Entrainment of mercury into homes of workers has also been reported (11). With chemical waste areas, the primary carriers probably would be children and pets, affecting transfers of soil and dust that could convert transient into constant exposure. Young children, with their tendency to explore the

world orally, are at special risk as demonstrated by dust from high-lead areas.

A study of a population in the vicinity of a lead smelting plant revealed the importance of transfer of dust from soil via the hands, resulting in oral ingestion (12). A correlation was observed in children between blood lead concentrations and average lead concentrations in air (Fig. 4). The fractional contribution of air-lead to blood-lead values was apparently higher in boys than in girls. This led to an investigation of indirect pathways from air to blood. It was discovered that hand contamination by lead dust was greater in boys than in girls and that sex differences in blood levels disappeared if blood lead was plotted against lead content of the

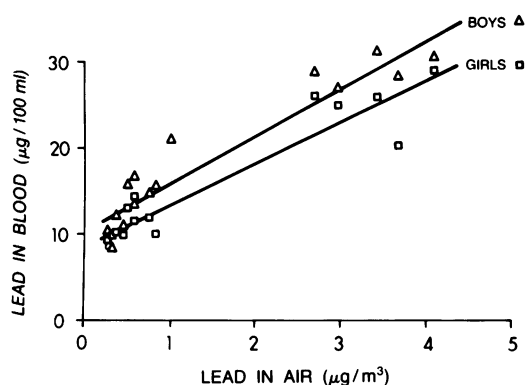


FIGURE 4. Apparent relationship between the concentration of lead in whole blood and the average concentration of lead in hair for 11 year-old boys and girls (12).

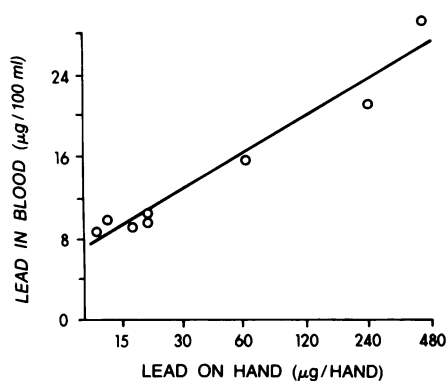


FIGURE 5. Relationship between mean concentrations of lead in whole blood and the amount of lead found on the hands of both boys and girls (12).

hands (Fig. 5). These results suggest that hand contamination is an important route of exposure for children living in lead contaminated areas. Hand-to-mouth transfer has been demonstrated as an important route of exposure in homes where interior lead paints were used (13).

Atmospheric transfer is a possible hazard not only because of direct contamination by soil and dust, but because of edible crops. Home gardens and area farms need to be evaluated for a complete assessment of sources of exposure.

Speciation of Metals

As metals journey through environmental and biological reservoirs, they can undergo chemical transformations that help determine both bioavailability and toxicity. Mercury is an outstanding example. The conversion of inorganic to methylmercury by microorganisms in the bottom sediment

of lakes and rivers (14,15), is a transformation that greatly enhances both bioavailability and toxicity. Chemical form may also determine solubility, volatility and other physical properties that ultimately contribute to toxicity because of the influence such properties exert on eventual environmental and tissue deposition. Mercury again provides an example. Mercury vapor penetrates the brain ten times as readily as ionic mercury (16).

Mercury is not the only metal whose toxicity is enhanced in its organic form (particularly the alkyl compounds methyl- and ethylmercury). Organic lead (tetraethyl) is notoriously toxic. Triethyl- and trimethyltin pose hazards far in excess of inorganic tin, which is relatively innocuous. A similar disparity applies to nickel. These organic forms are also much more neurotoxic, perhaps because of elevated lipid solubility that facilitates entry into the central nervous system. Whether the peculiar circumstances of certain chemical waste sites can effect such conversions is an unexplored question.

Exposure Assessment

Without a firm link to exposure indices, health assessment is carried out in a vacuum. Metals may present fewer analytical problems than many other ingredients of chemical waste sites, but they are hardly trivial. A number of errors that creep into these measurements—errors involved in collection, transport, storage and analysis—will not be dealt with in this discussion. In general, analytical methods measure the total elemental concentration of the metal. For certain metals, however, it is necessary to distinguish between the organic and inorganic forms and also to distinguish the different types of organic forms.

Measurement of human exposure to metals depends upon the analysis of suitable indicator media. The choice of these media, of course, is limited to available biological fluid or tissue. The assumption is that the concentration of the metal in the medium will reflect the body burden of the metal or the concentration of the metal in the target cells (17). When an individual has achieved steady state, the ratio between blood and tissue concentrations should be constant and there should also be a relationship to urinary excretion. Nevertheless, for a biological material to be a useful indicator of accumulation, especially for metals with long biological half-times, the ratio of blood to tissue concentration should be roughly constant during the accumulation phase. This is not true for all metals. In addition to blood, urine and hair, various other biological media have been used as indicators of accumulation of metals,

including saliva, teeth, nails, meconium, placental tissue and biopsy material. Comments will be made on indicator media for specific metals but limitations of space preclude an exhaustive treatment.

Lead

Blood lead is the most popular measure of recent exposure to lead. Furthermore, the contribution of various routes of intake of lead to the body burden have been estimated in terms of their contribution to an increase in blood lead (18). The major drawback to blood lead is that it is limited to the impact of recent exposure. In metabolic studies in humans with stable isotopes, Rabinowitz et al. (19) found the turnover time in blood to be only a few weeks. Lead in the dentine of deciduous teeth has been used as a measure of long-term accumulation of lead (20). Figure 6 illustrates the dramatic difference in tooth lead between children living in a district geographically remote from industrialization and a group in the United States where exposure is assumed to be high. Animal experiments indicate that the lead content of deciduous teeth correlates closely with average blood concentrations integrated over the period of tooth growth (22). It is not possible, however, to relate dentine values to peak concentrations in blood.

Hair analysis has received limited application in estimating lead exposure. Kopito et al. (23) noted large differences in hair concentrations between a control group (24 ppm) and lead-poisoned patients. A longitudinal analysis of hair (Fig. 7) indicates

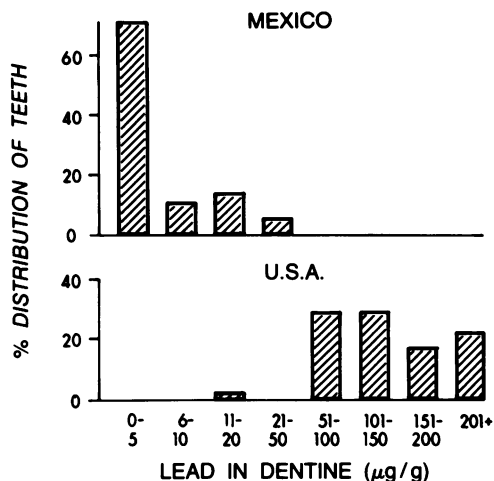


FIGURE 6. Distribution of lead concentrations in teeth from a contemporary population of Indians living in a nonindustrialized area of Mexico (36 samples), and in teeth from individuals living in Philadelphia (35 samples) (21).

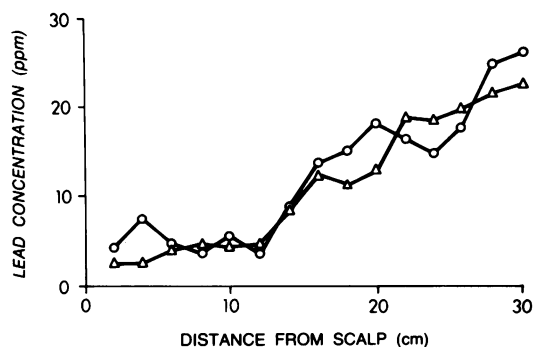


FIGURE 7. Concentration of lead in two strands of hair collected from the same person. Each point is the lead concentration in the preceding 1 cm segment measured from the scalp end (24).

that lead concentrations are lowest in freshly grown hair (near the scalp) and rise steadily with distance from the scalp. Renshaw et al. (24) suggested that such a pattern is consistent with lead entering the hair by deposition on its surface followed by diffusion into the hair structure and that sudden exposures to lead might be detected by a sharp peak in Pb concentration along the shaft. The correlation between blood and hair concentrations needs to be evaluated.

Cadmium

Autopsy data indicate that cadmium accumulates in body tissues over most of the human life span (Fig. 8). The urinary excretion parallels, on a group basis, the body burden. A more direct way of measuring body burden in individuals has become available in recent years. *In vivo* thermal neutron activation analysis reveals actual cadmium concentrations in liver and kidney tissue in human subjects. Figure 9 records the concentrations of cadmium in liver in nonexposed people, a group of office workers in a cadmium industry, a group of recent employees (those employed for less than 6 months) and, finally, a group of long-term employees (26). Significant differences in liver cadmium were detected between the long-term employees and the other groups. Since the apparatus can be transported to the area of a dumpsite, *in vivo* neutron activation may be worth considering if one suspects that substantial exposure to cadmium has occurred.

No detailed reports are available of the relationship between cadmium in hair and exposure indices or blood concentration. Since the levels of cadmium in hair are quite low there may be technical difficulties in making these measurements.

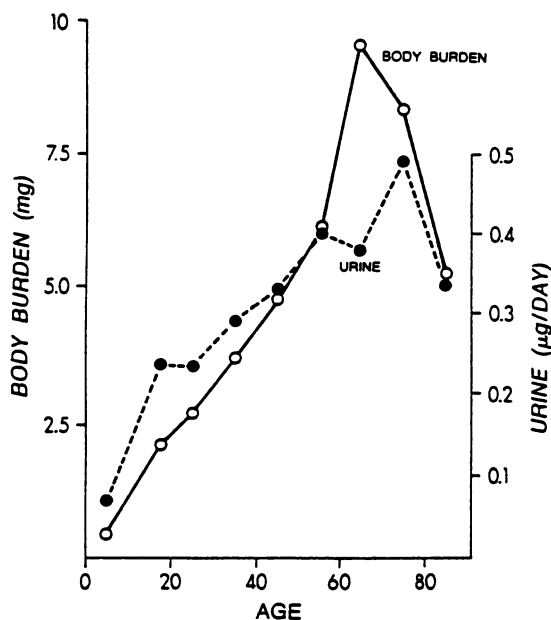


FIGURE 8. Estimated average body burden and the estimated average daily cadmium excretion in urine in nonsmoking Swedish males plotted as a function of age (25).

Mercury

In assessing the usefulness of various indicator media for mercury, careful distinction must be made between the different chemical and physical species of mercury.

Mercury Vapor. Urine is the indicator medium most widely used to assess human exposure to metallic mercury vapor. Figure 10 suggests a linear relationship between urinary mercury concentration and time-weighted average air concentrations in exposed workers. Smith et al. (27) also found a linear correlation between blood mercury and time weighted air concentrations. These studies were carried out in workers exposed for many years who probably had attained a steady state. Under steady-state conditions, one would expect to see linear relationships between levels in indicator media such as urine and blood and air concentrations. For shorter exposures or for measurements taken after the cessation of exposure, blood and urine concentrations will change at different rates. The half-time of mercury in blood after exposure to mercury vapor is relatively short, with a value of about 3 to 4 days (28). Mercury in urine, according to studies carried out on volunteers receiving tracer doses of mercury vapor, is not related directly to mercury in blood but probably reflects the kidney burden of mercury. The kidney is the main organ of accumulation for inorganic mercury, and the average half-

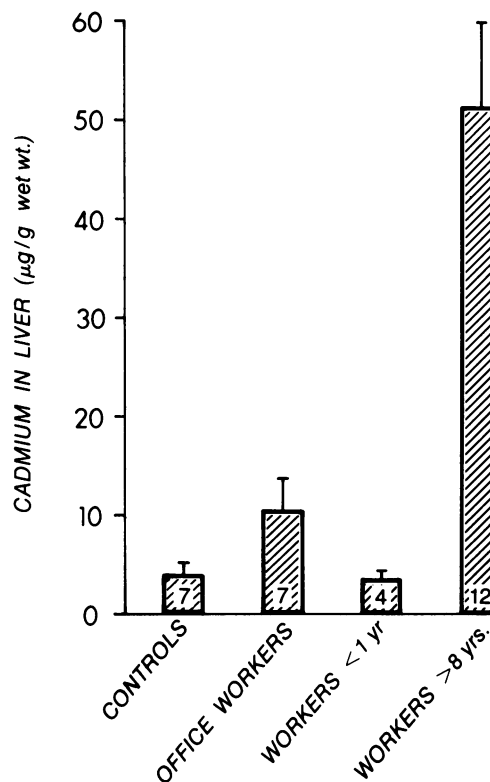


FIGURE 9. Cadmium content in liver in people grouped according to estimated exposure to cadmium in air. The number in each group is indicated in each column. The controls were workers in a water company (mean age 40 years); office workers (mean age 44 years) in a cadmium smelter plant; smelter workers (mean age 26 years) employed less than one year, and smelter workers (mean age 50 years) employed for 8 to 29 years. Cadmium in liver was measured by *in vivo* neutron activation analysis.

time in the tissue is 64 days according to tracer studies in volunteers (29). Since inorganic mercury is reduced to elemental mercury in tissues, mercury vapor is detectable in exhaled air (30,31). Treatment with nonintoxicating doses of ethanol increases the amount of vapor exhaled (31). Measurement of exhaled mercury after a standardized oral dose of ethanol might provide a measure of inorganic mercury accumulation. Thermal neutron activation is, in principle, applicable to mercury in tissues and should be an excellent method for measuring the burden of mercury in the kidneys after exposure to mercury vapor. No reports have yet appeared in the literature on the application of this technique.

Methylmercury. Observations on individuals ingesting tracer doses of methylmercury, as well as in others taking larger measured doses of methylmercury indicate that a constant fraction of the

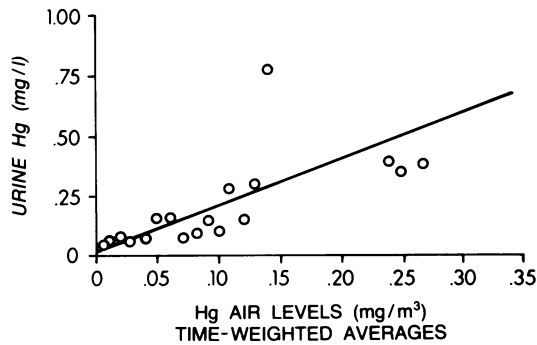


FIGURE 10. Relationship between the average urinary concentration of mercury and the time weighted average air concentrations for groups of workers occupationally exposed to mercury vapor in the chlorine industry (27).

body burden (approximately 5%) is found in the blood compartment (32,33). This percentage seems to be more or less independent of the total dose of methylmercury. Furthermore, the ratio of brain, the target organ, to blood seems to be constant for most animal species, although the actual value of the ratio is species-dependent. Thus, measurements of methylmercury in blood serve as a measure of body burden and of current average brain concentrations (5).

Since the biological half-time of mercury in blood is about 50 days, it will take an individual about one year to attain a steady state. Under these circumstances, blood concentrations are proportional to average daily intake (34). When individuals experience intermittent exposure, there is a need to recapitulate past blood concentrations since methylmercury may produce irreversible brain damage. It turns out that measurement of mercury along the hair shaft accurately reflects prior blood concentrations of methylmercury.

The relationship between hair and blood concentrations of total mercury in an individual exposed to methylmercury is illustrated in Figure 11. The blood samples are plotted according to their date of collection. The hair was divided into 1-cm segments measured from the scalp, and each centimeter was measured for total mercury. Since hair grows at approximately 1 cm/month, each segment represents 1 month's growth. The values for those segments are plotted on this figure according to the date of formation of that particular segment. There is excellent correspondence between the average mercury concentration in 1 cm of hair and the blood concentration at the time of formation of the hair sample, indicating that at the time of hair formation at the root, blood enters the hair in proportion to the concentration in the blood. This concentration

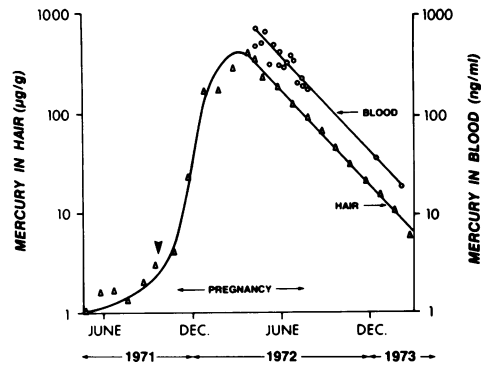


FIGURE 11. Relationship between concentration of mercury in 1 cm segments of hair and in samples of blood collected at the time of formation of the one centimeter segment. The hair sample was collected in early 1973 and analyzed centimeter by centimeter measured from the scalp. The date of formation of the hair was estimated from a growth rate of 1 cm/month (35).

ratio of hair to blood has a value of approximately 250. Once the mercury has entered the hair, it remains at a stable concentration (35). In this particular example, the hair measurements allowed recapitulation of blood concentrations during the preceding two years and, important in this case, throughout the period of pregnancy.

Hair analysis has now become an almost routine procedure for assessing the exposure of populations to methylmercury (36). Seasonal exposure to methylmercury in a group of North American Indians is illustrated in Figure 12. These individuals ingested

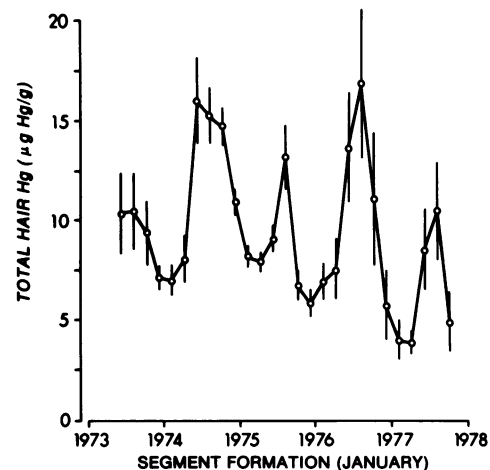


FIGURE 12. Seasonal changes in mercury concentrations in hair in individuals consuming methylmercury in fresh water fish. One centimeter segments of hair were analyzed for total mercury. The mercury concentration is plotted against the date of formation of each segment of hair assuming an average growth rate of 1.15 cm/month (37).

methylmercury from fish in the summer months only. The peak values in hair concentrations are clearly visible and repeated year by year. Hair analysis could be equally useful in assessing the pattern of exposure in people living in or near a dump site where exposure to methylmercury is suspected.

Health Effects

Attempts to determine adverse health effects from the kind of metal exposures likely to be encountered in the vicinity of chemical waste sites are subject to the same problems that bedevil epidemiologic toxicology directed towards other substances. How to separate one from any concurrent exposures and how to select an appropriate control group are universal questions. The early symptoms of intoxication, moreover, no matter the class of substances, are likely to be vague and nonspecific. Only if exposure is severe enough to erupt into frank clinical disease is a specific agent likely to be suspected.

A possible solution to this dilemma is to decide on what constitutes a "critical effect" and proceed to develop or to choose sensitive, objective, specific tests. Such a course, naturally, is easier to prescribe than to fulfill. It is further complicated by the attention we have to pay to susceptible subgroups such as the very young. To facilitate such a choice we will try to review for each of the three metals, relevant early symptoms, possible functional (and quantifiable) tests, and associated biochemical indicators.

Lead

Most objective tests available for evaluating the adverse consequences of lead exposure depend upon lead's action in disrupting the pathways of heme synthesis (Tables 2 and 3). Increased δ -aminolevulinic acid in urine, decreased δ -aminolevulinic acid dehydratase activity in red cells or, more recently, elevated free erythrocyte protoporphyrin are used as early warning signs of the biochemical derange-

Table 2. Summary of lowest PbB's associated with observed biological effects in various population groups.^a

Lowest observed effect level, $\mu\text{g Pb}/100\text{ mL blood}$	Effect	Population group
10	ALAD inhibition	Children and adults
15-20	Erythrocyte protoporphyrin elevation	Women and children
25-30	Erythrocyte protoporphyrin elevation	Adult males
40	Increased urinary ALA excretion	Children and adults
40	Anemia	Children
40	Coproporphyrin elevation	Adults and children
50	Anemia	Adults
50-60	Cognitive (CNS) deficits	Children
50-60	Peripheral neuropathies	Adults and children
80-100	Encephalopathic symptoms	Children
100-120	Encephalopathic symptoms	Adults

^aAdapted from Table II of EPA Ambient Water Criteria for Lead (18).

Table 3. No detected levels in terms of PbB.

No detected effect level, $\mu\text{g Pb}/100\text{ mL blood}$	Effect	Population
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	Anemia	Children
40-50	Peripheral neuropathy	Adults
50	Anemia	Adults
50-60	Minimal brain dysfunction	Children
60-70	Minimal brain dysfunction	Adults
60-70	Encephalopathy	Children
80	Encephalopathy	Adults

^aAdapted from Table II of EPA Ambient Water Criteria for Lead (18).

ments produced by lead. Some investigators report a gradual change in these parameters as the blood lead concentrations increase (38). Such a function makes it difficult to define a boundary between abnormal and normal values.

Other investigators, however, have attempted to define a control range of values and to classify individuals on that basis. Roels et al. (39) designated abnormal values of free erythrocyte protoporphyrin (FEP) as those beyond the upper 95% confidence limit of a control group. A concentration-response relationship based upon FEP cut-off levels (82, 83 and 68 $\mu\text{g}/100\text{ mL}$) for children, women and men, respectively, and blood lead levels (PbB) is given in Figure 13. Roels et al. (39) noted that these curves indicate that "the susceptibility of the heme biosynthetic pathway to lead, as reflected by FEP is in the order children > women > men." Indeed, 50% of the children already exceed the FEP cut-off value when PbB reaches 25 $\mu\text{g}/100\text{ mL}$, 50% of the women when PbB reaches 28 $\mu\text{g}/100\text{ mL}$, and 50% of the men when PbB reaches 35 $\mu\text{g}/100\text{ mL}$.

Lead inclusion bodies in cell nuclei have been reported as an early effect of lead in animal experiments (40). Goyer (41) has suggested that the urinary excretion of these bodies might serve as an early objective measure of adverse lead exposure.

The consequence of lead exposure which is most difficult to assess is its central nervous system toxicity. Low-level, asymptomatic lead exposure has been associated, in children, with lowered performance on psychological tests and conduct disorders in the classroom. A steady stream of well-

controlled experiments, such as that by Needleman et al. (42), have proved convincing enough to induce public health agencies to view blood lead values of 30 $\mu\text{g}/\text{dL}$ as risky. Needleman's results were based on dentine lead analysis and showed clear deficits in asymptomatic children with the higher values. Equivalent findings have been reported from England and Germany. Most intriguing of all are the data from that experiment suggesting a dose-response relationship between tooth lead and classroom behavior ratings by teachers, a function not consistent with a threshold.

Risk zones for adults have also fallen sharply toward lower values as more subtle consequences are pursued. The reports of the group in Helsinki at the Institute for Occupational Health are especially provocative (43). Their data, like newer data from the United States, suggest that blood lead concentrations of 50 $\mu\text{g}/\text{dL}$ are associated with diminished test performance, increased psychological and somatic complaints, and decreased nerve conduction velocity.

Cadmium

The detection of early adverse effects of cadmium has been a special focus of Swedish investigators (3). They have identified the kidney as the first tissue in which adverse effects are evident and have suggested that disturbances in renal tubular function form the critical effect, i.e., the first early warning sign of incipient cadmium damage. Such disturbances are manifested as increased urinary excretion of small molecular weight proteins, those proteins such as β_1 microglobulin that are normally filtered and reabsorbed in the proximal tubule.

Buchet et al. (44) investigated the presence of specific proteins in urine samples of cadmium exposed workers. Abnormal values were defined as those exceeding the upper 95% confidence limits of values from a control group, a definition used previously to define abnormal amino acid excretion in cadmium-exposed workers (45). The percentage of individuals showing normal values for certain specific proteins was compared with the urinary excretion of cadmium. The urinary excretion of both large (albumin, immunoglobulin) and small (β_2 microglobulin) were increased in a dose-related fashion. Several enzymes also showed increased activity in urine (β -galactosidase, alkaline phosphatase). Buchet et al. (44) concluded that occupational exposures to cadmium affect both glomerular and renal tubular function and that these effects begin to manifest themselves in urinary excretion of cadmium in the range of 10–20 $\mu\text{g Cd/g creatinine}$. However, when their results are examined graphically according to

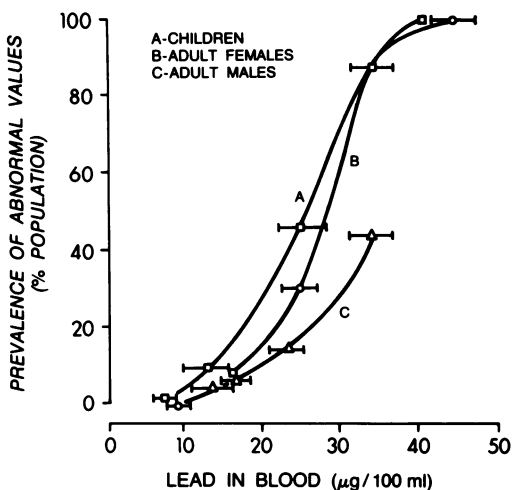


FIGURE 13. Relationship between the percentage of abnormally high free erythrocyte protoporphyrin and average blood lead levels in (A) children, (B) adult females and (C) adult males (39).

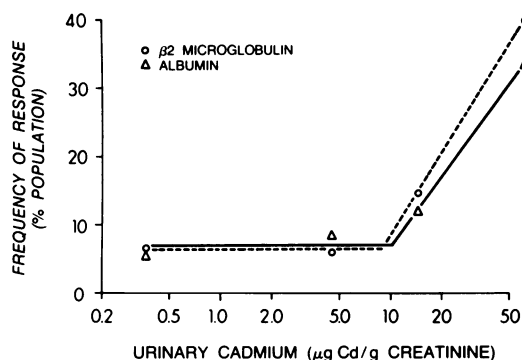


FIGURE 14. Relationship between the percentage of abnormally high urinary values of (Δ) albumin or (\circ) β_2 microglobulin and the average urinary excretion of cadmium in workers in cadmium smelter plants and in "control" workers employed in a number of factories. A "control" worker was judged to have no occupational exposure to cadmium and the urinary excretion should be less than 2 $\mu\text{g/g}$ creatinine at the time of the study. The data were taken from Figure 1 of Buchet et al. (44). The two straight lines were drawn according to hockey stick analysis (46).

hockey stick analysis, effects appear detectable at urine concentrations below 10 $\mu\text{g Cd/g}$ creatinine (Fig. 14). The horizontal line indicates "background" frequency. The rising line indicates increasing frequency of abnormal values due to cadmium exposure. The intersection of the two lines is the "practical threshold" at which effects due to cadmium emerge above background. There is considerable statistical uncertainty about these practical threshold values. The 95% confidence limits were estimated to be: albumin, 4.2–26; β_2 microglobulin, 3.5–23; and galactosidase, indeterminate. These analyses are consistent with the conclusion of Buchet et al. (44) but suggest that adverse effects may occur at lower urinary concentrations. These values are in the same range as those estimated by an expert group (47) to be associated with accumulation of a critical concentration of cadmium in kidney tissue. It should be stressed, however, that urinary cadmium offers only a gross index of cadmium accumulation and is not a useful predictor of effects on an individual basis. Piscator and Pettersson (48) have recommended that the measure of choice for screening is β_2 microglobulin in urine. More recently, Lauwerys et al. (49) have noted that β_2 microglobulin is unstable in acid urine and recommend measurement of retinal binding protein; the latter gives the same information but is stable in urine samples.

Mercury

Adverse health effects due to mercury exposure depend upon the specific chemical and physical forms

of this element. Mercury exists in three oxidation states: metallic (Hg^0), mercurous (Hg_2^{2+}), and mercuric (Hg^{2+}). The mercuric form is able to form stable organometallic compounds in which mercury is covalently linked to a carbon atom, e.g., methylmercury or phenylmercury compounds. In theory, all these principal forms of mercury may be encountered in dump sites. In the Hackensack Meadowlands recreational area, situated some 6 miles from the center of New York City, an estimated 600 tons of mercury were dumped. Both metallic mercury and phenylmercury compounds were found to be present. We will discuss only the major distinction: inorganic versus organic mercury.

Inorganic Mercury. Mercuric salts are potent kidney poisons. The estimated single oral dose of mercuric chloride to produce death in an adult human subject is about 1 g (50).

The mercurous salts, due to low solubility, represent a minimal hazard. However, children ingesting mercurous chloride (calomel) in teething powder developed a syndrome known as acrodynia (painful extremities) or Pink Disease (51). The signs and symptoms include bluish-pink hands and feet, crimson cheeks, profuse sweating, painful joints, photophobia, glove-and-stocking paresthesias, irritability, and other nervous system disturbances. Although only a small fraction of the children exposed to inorganic mercury developed overt toxic reactions, many must have suffered subclinical toxicity. Phenylmercury may be less potent. In a recent exposure of an estimated 6000 infants to a phenyl mercury compound, only three or so developed acrodynia by classical criteria, although many more showed evidence of some of the signs (52).

Mercury vapor has been known for centuries to produce a distinctive triad of erethism, tremor and gingivitis (53). Erethism is a disturbance of the central nervous system leading to a number of psychological effects: excessive shyness, emotional lability, irritability, and anxiety. Tremor manifests itself particularly in the extremities, the tongue and eyelids, and becomes even more exaggerated when the patient is under observation (compulsion tremor). The total syndrome of mercurialism is not always diagnosed easily.

Diagnosis is much more difficult during the earliest phases of mercury toxicity because the manifestations are nonspecific and could arise from causes other than mercury exposure. This problem is exemplified by dose-response data taken from a large epidemiological study (27). It found an increase in the frequency of subjective complaints such as insomnia, loss of appetite, shyness and weight loss to be the earliest changes associated with occupational exposure to mercury vapor. These effects

were seen at time-weighted air concentrations of about $100 \mu\text{g}/\text{m}^3$, corresponding to an average urinary concentration of about $200 \mu\text{g}/\text{L}$. Russian studies have claimed the existence of nonspecific "neurasthenic" effects at concentrations far below these levels (54).

Wood et al. (55) demonstrated marked shifts in both the amplitude and frequency spectrum of tremor in victims of occupational mercury exposure (Fig. 15). Langolf et al. (56) adapted this test system for quantitative measurement of tremor in chloralkali workers. The individual grasps a special electromechanical device which records tremor at various

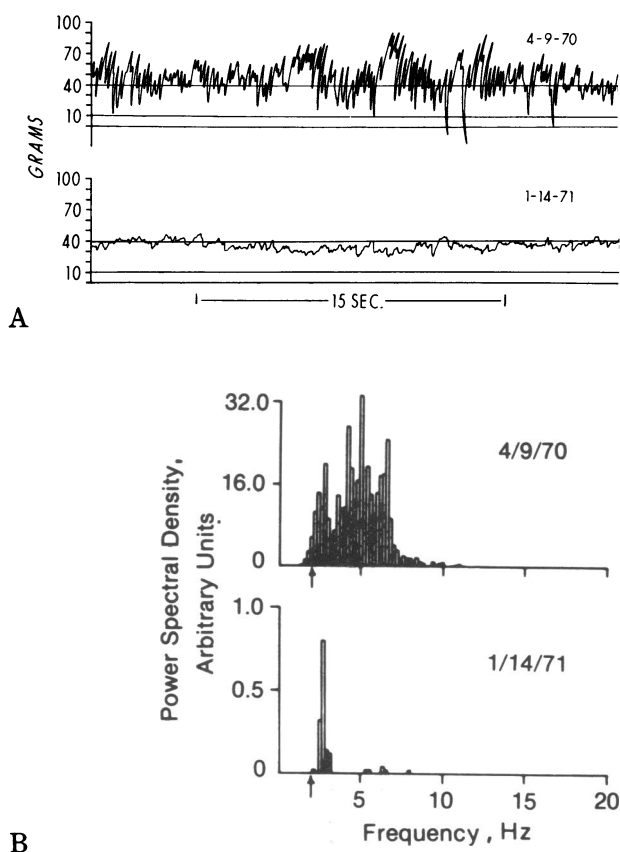


FIGURE 15. (A) Tremor tracings from a woman exposed to mercury vapor in a plant using metallic mercury to calibrate pipets. The upper tracing was recorded when the victim first was seen at the hospital. The lower tracing was recorded 9 months later, with no intervening exposure. Recordings were made by having the patient rest the index finger in a Lucite slot attached to a strain gauge while attempting to maintain a force between 10 and 40 g. (B) Tremor spectra corresponding to the tracings in (A). Strain gauge output was amplified and fed to the analog-digital converter of a PDP-12 computer. The power spectrum was calculated by a Fast Fourier Transform. Note the multiple peaks in the spectrum corresponding to the more severe tremor (55).

weight loads on the arm. A power spectral analysis is made of the recordings. Shifts in the spectrum were not detected until urinary mercury concentration exceeded $500 \text{ mg}/\text{L}$.

The approach of measuring neurological signs may be contrasted to the one adopted by Buchet et al. (44). These investigators attempted to identify and measure specific proteins in the urine, using the same approach adopted for cadmium. Their data are displayed as a concentration-response relationship plotted according to the hockey stick model (Fig. 16). The high molecular weight proteins such as albumin but not the small molecular weight proteins such as β_2 microglobulin, exhibited increases in frequency of abnormal values at the higher urinary concentrations of mercury. This test distinguishes dramatically between effects due to cadmium (both low and high molecular weight proteins) and effects due to mercury. This hockey stick analysis indicates effects on urinary proteins become detectable at urinary levels of $50 \mu\text{g}/\text{L}$ or even lower. Such levels are lower than urinary concentrations associated with objective measures of tremor. Unfortunately, the history of exposure to mercury vapor was not stated.

Organic Mercury. Methylmercury produces no biochemical or physiological disturbances such as proteinuria, clearly associated with exposure. At present, we have to rely entirely on neurological examinations or on subjective complaints by the patient. It will therefore remain extremely difficult to detect early health deficits in a population exposed to methylmercury from a dumpsite. Measurements of methylmercury in blood or in hair combined with other epidemiological data will have to be used to assess the associated health risks.

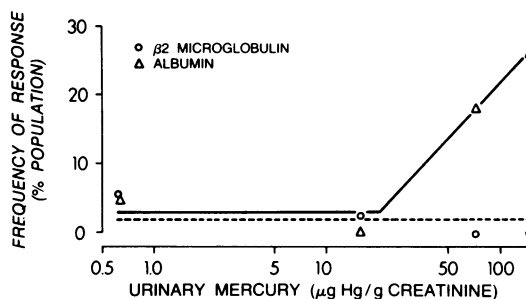


FIGURE 16. Relationship between the percentage of abnormally high urinary concentrations of (○) β_2 microglobulin and (Δ) albumin and average urinary excretion of mercury in 63 workers in two chloralkali plants and in 88 "control" workers. The "controls" were judged not to have occupational exposure to mercury vapor and the urinary excretion of mercury was less than $5 \mu\text{g}/\text{g}$ creatinine. The straight lines were drawn according to hockey stick analysis (46). The data were taken from Buchet et al. (44).

Methylmercury compounds selectively damage certain functions of the central nervous system producing sensory deficits such as paresthesia, tunnel vision and loss of hearing, and motor deficits manifested by ataxia and dysarthria. Symptoms and signs of poisoning as a function of the concentration of methylmercury in blood are depicted in Figure 17. Paresthesia is the first complaint to respond to increasing blood levels of methylmercury and has the lowest practical threshold blood level. Unfortunately, paresthesia alone cannot be used to diagnose methylmercury poisoning in suspected victims because it may be caused by many other factors. Biochemical tests corresponding to those used with lead, or physiological changes such as proteinuria, used with cadmium or mercury vapor, are not available as early indicators of methylmercury poisoning.

Prenatal life and infancy are the stages of the life cycle most sensitive to methylmercury, which can produce severe derangement of the developing central nervous system (58,59). At the lowest exposure levels, consequences such as delayed achievement of developmental milestones and mild neurological abnormalities are observed (60). Clarkson et al. (61) have estimated that the prenatal organism is two to four times more sensitive than the adult organism to methylmercury but the ratio is based on a comparison of mild (paresthesias) with much more severe (retardation) effects.

Organomercurials, other than the short chain alkylmercurials, rapidly break down to inorganic mercury in the body. They act primarily on kidney function though cases of overt human poisonings are rare (62). Even the relatively slow breakdown

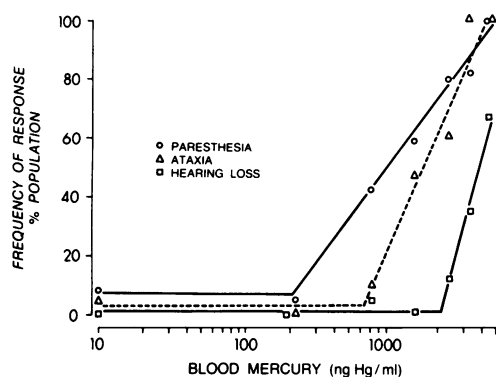


FIGURE 17. Relationship between the frequency of (○) paresthesia, (Δ) ataxia or (□) hearing loss and the average blood concentration of total mercury in a population that had been exposed to methylmercury up to 65 days prior to blood sampling (57). The lines are drawn according to hockey stick analysis (46).

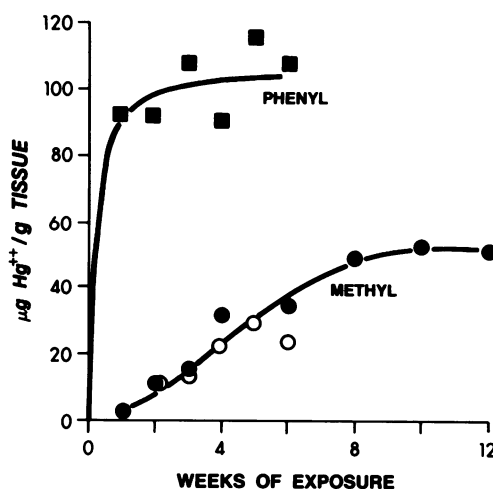


FIGURE 18. The increase in concentration of inorganic mercury in the kidneys of rats dosed repeatedly with phenyl- or methylmercury compounds (63,64).

of methylmercury as compared to phenylmercury (Fig. 18), however, eventually leads to high kidney levels of inorganic mercury. In the animal experiments depicted in this figure, kidney levels of inorganic mercury substantially exceeded those levels (20-30 $\mu\text{g Hg/g}$ wet weight) associated with severe damage from a single dose of mercuric chloride. No gross kidney damage was observed after the organomercurials. Tolerance to inorganic mercury takes place slowly with accumulation (65). Nevertheless, one might expect to see changes in urinary excretion of specific proteins as reported by Buchet et al. (44) after human exposure to mercury vapor under circumstances in which kidney accumulation is also slow.

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