

HUMAN HEALTH CONSEQUENCES DUE TO LEAD EXPOSURE
FROM AUTOMOTIVE EMISSIONS

This third, dull lead, with warning all as blunt, -
"Who chooseth me must give and hazard all he hath."-

The Merchant of Venice
II, VI, 8-9
Shakespeare (1596/7)

Kathryn Mahaffey
Terri Damstra
Warren T. Piver
Herbert S. Posner
Hans L. Falk (Chairman)

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Recommendation and Conclusion

Lead has been recognized as a toxic element and at high dosage levels its toxicity is most significant for the central and peripheral nervous system. The prevalence of non-industrial lead toxicity is particularly apparent in children of young age.

In our deliberations the committee has looked at available data regarding lead emission from automobile exhausts to learn about the physical and chemical dimensions of the particulates containing lead. It was learned that not all lead leaves the auto with the exhaust and that the particulate matter has different physical properties depending on age or performance of engine or exhaust systems. This information was valuable regarding the fate of the particulate matter in air. (See Chapter 1, Sections 1.0 to 1.3).

For lead no sink has been discovered that would remove lead from potential human contact even though much of the particulate matter is of a size that would fall out rapidly and of chemical composition which makes the lead less water soluble than when it was emitted. Lead in dust can be ingested and absorbed particularly by young children following mouthing of objects or can be swallowed with food if not carefully washed off. Once in the soil it is not readily taken up by most food plants. (See Chapter 1, Sections 2.0 to 2.2.3).

Regarding intake of lead by humans, greater emphasis is put on that portion ingested compared to that inhaled. Many factors are involved in the absorption of the lead from the gastro-intestinal tract and the degree of absorption is much lower than from the lung for adults. For children the percentage reduction of ingested and inhaled lead does not differ greatly on the basis of data currently available.

Although adequate data are available on the absorption in the adult, this does not apply necessarily to young children where data are sparse, but the absorption

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of lead appears to be higher. It may not be very important to distinguish absorption via the gastro-intestinal or the respiratory tract when in either case lead could have originated from auto exhaust. (See Chapter 3).

The biochemical interactions of lead in mammalian species have been well studied to serve as explanations of observed effects and also to be of use in monitoring health effects and exposure to lead. (See Chapter 2). From these studies it became apparent that blood lead determinations are not as useful as previously assumed, at levels of relatively low increases. Blood and urine determinations of some of the biochemical changes together with blood lead determinations supply a much better picture of people's past or present exposure and ill-health. Biochemical lesions can be observed where blood lead levels were considered as "normal" for that moment. Many disagreements are based on the correlation of past lead exposure with blood lead levels and neurologic symptoms. Other shortcomings in correlation of mental retardation or hyperactivity in children with blood lead levels become obvious on reviewing the literature while correlations with anemia or increased susceptibility to infections have been established by animal studies. (See Chapter 4).

The Committee agrees with Sir A. Bradford Hill (1):

"All scientific work is incomplete whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us freedom to ignore the knowledge we already have or to postpone the action that it appears to demand at a given time".

Our recommendation, therefore, is to phase out lead in gasoline by reducing its content as has been proposed by the U.S. EPA and by many other developed countries, or to hold the maximum allowable concentration at a lower level as has been in effect in most European countries for some time (2).

Even if current levels of lead exposure for children or future generations are too low at the time of writing to have a clear cut adverse effect on them, it may only be a matter of time until a critical level could be reached for some and disease would result because the lack of a sink for lead allows its buildup in the immediate environment of children. (See Chapter 1, Section 3.0). If lead is allowed to remain in gasoline even at lower levels, it would be imperative to prevent its spread into the environment by filtration or other devices.

Replacement of lead by other fuel additives or by engineering modifications to the engine or exhaust system should have reduced adverse health effects as its primary consideration in the evaluation for performance vis-a-vis lead. (See Chapter 5).

Recommendation and Conclusion

References:

1. Hill, A. B. The environment and disease: Association or causation. Presidential Address. Proc. Roy. Soc. Med. (1965) 58: 299--.
2. Groupe d'étude international du plomb et du zinc, Les effets de l'addition de plomb a l'essence, examen de la situation actuelle. LZ/73/1 7/18/1973, 1-40.

1. ENVIRONMENTAL TRANSPORT AND TRANSFORMATION OF AUTOMOTIVE EMITTED LEAD

This portion of the report is concerned with the fate of particulate lead compounds emitted to the atmosphere from the combustion of leaded gasoline in spark-ignition engines. As this term will be used here, the fate of particulate lead has the following description. It is concerned with not only how these emissions are initially partitioned between air, water, and solid phases when discharged from the tailpipe, but also how this partitioning varies with time due to the physical-chemical properties of these emissions and to environmental transport and transformation processes which act upon them.

Because there are many properties and processes which influence the fate of exhaust emitted lead particulate matter, use will be made of a mass balance as a simple method of keeping track of what properties and processes influence how these particulate lead emissions are partitioned. For a given geographical area, this mass balance can be written as:

$$\left[\begin{array}{l} \text{Rate of Lead Particulate} \\ \text{Emission into Atmosphere} \\ \text{by Motor Vehicles Moving} \\ \text{Through Geographical Area} \end{array} \right] - \left[\begin{array}{l} \text{Rate of Lead Removal} \\ \text{from Geographical} \\ \text{Area by Physical and} \\ \text{Chemical Processes} \end{array} \right] = \left[\begin{array}{l} \text{Rate of Accumulation} \\ \text{of Lead Within this} \\ \text{Geographic Area} \end{array} \right]$$

In essence, this approach of cataloging the properties and processes which influence the partitioning of lead particulate emissions is similar to that used by Huntzicker, et al. (1975) in their material balance study of automotive-emitted lead in the Los Angeles Basin.

1.0 Rate of Lead Particulate Emission into the Atmosphere by Motor Vehicles Moving Through a Geographical Area

Particulate emissions from mobile sources amount to about a million tons/year, whereas CO is emitted at a rate of about 66 million tons/year.

hydrocarbons at a rate of 12 million tons/year, and nitrogen oxides at a rate of 6 million tons/year (PHS Publication - 1968). Particulate emissions from mobile sources are composed of both organic and inorganic substances such as lead, carbon, halogens, iron, oxides of metals, and oil mist. When leaded fuel is used in spark-ignited engines, lead compounds can make up a substantial percentage by weight of the particulate emission. Hirschler and his coworkers (1957, 1964) estimated that lead compounds comprised 58 to 78% by weight of particles less than 5 microns in size (fine), and comprised between 34 to 60% by weight of particles greater than 5 microns in size (coarse particles).

The factors which effect both the rate of particulate lead emissions and the physical-chemical properties of these emissions are: fuel lead additive content; the driving speed or mode of driving; and the design and operational features, maintenance, and age of both the engine and the exhaust system. The important physical-chemical properties of these particulate emissions are: total amount emitted, shape, and size distribution of the particles; chemical composition of these particles as a function of particle size; and the location of the lead compounds in a cross-sectional slice of the particle. The particle size is an important characteristic. The most commonly used index of particle size which is reported in experimental studies is the mass median equivalent diameter (MMED). This property is determined from the log-normal size distribution of particles such that half the mass lies on either side of the MMED (PHS Publication - 1970). Therefore, this is an average particle size determined on the basis of total mass. Returning to the material balance equation, the physical-chemical

properties of emitted lead containing particulate emissions have a profound influence on both the rate of removal and the rate of accumulation within a geographical area.

1.1 Lead Content of Gasolines

The average lead contents of gasolines sold at gas stations, on a national basis have been determined by Jungers, et al. (1975). These average contents are: 600 $\mu\text{g/ml}$ (2.3 gm Pb/gal) for premium grades; 494 $\mu\text{g/ml}$ (1.86 gm Pb/gal) for regular grades; and 134 $\mu\text{g/ml}$ (0.5 gm Pb/gal) for low-lead grades. In many of the experimental studies on characterization of lead particulate emissions a special type of test fuel, Indolene, is used. Two types of Indolene fuel are used, Indolene HO 0 which contains no lead, and Indolene HO 30 which contains 3 ml tetraethyl lead (TEL)/gal.

1.2 Driving Speed or Mode of Driving

A summary of data on how both constant driving speed and the 7-mode Federal Test Cycle (Federal Register - 1966, 1968, 1970) effect the physical-chemical characteristics of lead particulate emissions has been given by Springer (1973). Since this review, several additional studies on the characterization of lead particulate emissions have been reported by Moran, et al. (1971), Habibi (1973), Ter Haar (1972), and Boyer and Laitinen (1975). This summary is given in Table 1.

Before presenting this data summary, it is necessary to include several comments about these experimental programs and their results. Measurements of particulate emissions have been made with engines mounted on dynamometers, and with engines driven on chassis dynamometers. Experiments have been performed for constant vehicle speeds, accelerating engines, decelerating

engines, and for engines operating under definite driving cycles. It has been demonstrated that at a constant speed or cruise condition, lower emission rates are observed than when an engine is accelerating or decelerating. However, as the cruise speed increases, the rate of emissions increases but the MMED of the particulate emissions decreases. During acceleration from a constant speed condition, the emission rate and the MMED of the particles increases because the rapid change in speed tends to dislodge the layer of exhaust emission deposits which has been built up along the length of the exhaust system when the engine was operating at a constant speed. For this reason, the emission rate measured in gm/mile (McKee and McMahon - 1960, Hirschler and Gilbert - 1964) increases rapidly during acceleration. Continued high rates of speed may initially discharge greater quantities of lead than is being burned. Eventually the rate drops to a stable level. After this type of driving, the exhaust system will begin to build up another deposit layer. Emission rates for an initially cold engine are much higher than for an engine which has been stopped after it has warmed up and then restarted again (hot start versus cold start). In addition, Ninomiya, et al. (1970) demonstrated that several test cycles were necessary for the emission rate to drop to a stable level.

For these reasons, the 7-mode Federal Test Cycle and the Federal Mileage Accumulation Schedule (Federal Register - 1968) were developed. By using these two procedures, deposits of exhaust materials are stabilized and the measurement of emission rates would more nearly reflect actual types of driving patterns and situations. Even with these recognitions and standardizations, individual drivers and individual engines will produce their own

unique sets of results for emission rates and particulate characteristics. This needs to be remembered when using these results to simulate the characteristics of particulate exhaust emissions for the present U.S. motor vehicle fleet.

Before leaving the subject of how driving speed affects particulate lead emissions, several additional observations are important to mention. During normal driving operations about 1/3 of the total lead used in combustion remains in the vehicle (Hirschler and Gilbert - 1964). Part of the lead is deposited on the surfaces of the engine-exhaust system and part ends up in the lubricating oil due to leakage around the piston rings.

In summary, therefore, the following general comments about how driving speed or mode of driving effect the physical-chemical characteristics of particulate emissions can be made:

1.2.1 Leaded Fuels

1. Lead particulate emission rate increases as constant vehicle speed (cruise) increases.
2. At slower constant vehicle speeds, the majority of lead particulate emissions are greater than 5 microns MMED; at higher constant vehicle speeds, the majority of lead particulate emissions are less than 0.5 micron MMED.
3. As the lead content of gasoline increases, the weight concentration of particles and the emission rate increases for all types of driving modes.
4. For the 7-mode Federal Test Cycle lead emissions increase as fuel lead content increases. It should be remembered that this test

procedure includes constant vehicle speed operation, acceleration, and deceleration types of driving. Therefore, the emission rate for the 7-mode Federal Test Cycle is an average rate for all of these different types of driving operations. It is well demonstrated that acceleration-deceleration produce higher emission rates than cruise conditions, but it would be difficult to compare these two types of driving on an absolute basis.

5. The major chemical form of lead in particulate emissions for all types of driving conditions is the mixed halide, PbBrCl . Other minor constituents are $\text{PbCl}_2 \cdot \text{PbClBr}$, $(\text{PbO})_2 \text{PbBr}_2$, $\text{PbO} \cdot \text{PbSO}_4$, PbSO_4 , $\text{Pb}_3(\text{PO}_4)_2 \cdot \text{PbClBr}$, and $\text{PbClBr} \cdot \text{NH}_4\text{Cl}$. Fe_2O_3 is also a major constituent of large particulate emissions. In addition unspecified carbon compounds are also part of these emissions.
6. The analytical identification of $(\text{PbO})_2 \text{PbBr}$, PbSO_4 , and $\text{Pb}_3(\text{PO}_4)_2$ and $\text{Pb}(\text{OH})\text{Br}$ has been challenged by Heidel and Desborough (1975).
7. Morphologically particulate emissions are made up of a carbon core which holds adsorbed to it polynuclear aromatics (4-6 membered rings - Boyer and Laitinen - 1975). This core is surrounded by the lead compounds and double salts which have condensed from the vapor phase (Sampson and Springer - 1973 and Linton et al. - 1976).

1.2.2 Unleaded Fuels

1. Particulate emission rates are generally lower than for leaded fuels for comparable driving conditions.
2. Chemically, these particles are mostly carbon with adsorbed multi-ring polycondensed aromatics which are formed during the combustion process.

3. The emission rate increases as the aromatic content of the fuel increases.

1.3 Design Features, Operating Conditions and Age of Both the Engine and the Exhaust System

Variations in air/fuel ratio and spark timing have very little effect on the emission rate and the characteristics of particulate emissions (Sampson and Springer - 1973, Ganley and Springer - 1974). In Table 1, however, it is adequately demonstrated how cold start versus hot start conditions plus the number of driving cycles influences the rate of exhaust particulate emissions (Ninomiya, et al. - 1970).

The design, operating conditions, and age of the engine-exhaust system have been shown to have an important influence on the characteristics of particulate lead emissions. The axial temperature along the length of the exhaust system is a function of the driving speed (Edwards -1973). Sampson and Springer (1973) and Ganley and Springer (1974) have demonstrated how axial temperature and exhaust gas temperature influences emission rate and weight concentration of particulate emissions. For a cruise condition of 55 mph, and Indolene HD 30 leaded fuel, there was a rapid increase in particulate weight concentration for an exhaust gas temperature drop between 640 - 470° F. This weight increase was attributed to the condensation of lead salt vapors onto a carbon particle core. X-ray diffraction identified this material as a mixture of $PbCl_2$ and $PbBrCl$. The particulate weight concentrated remained constant from a temperature range of 470 - 250°F. Below 250°F, the weight increased again, presumably due to condensation of high molecular weight organic compounds which boil in this temperature range, from the exhaust gases.

Organic chemicals which boil in this temperature range have significant vapor pressures. Therefore, after a short period of exposure to the environment outside the exhaust system, the particle would be composed of its carbon/polynuclear aromatic core, surrounded by a lead salt shell.

Earlier, Hirschler and his coworkers (1957, 1964), and more recently Habibi (1970, 1973) have examined how the age of the engine-exhaust system affect both the rate and physical-chemical characteristics of particulate emissions from the combustion of leaded fuels in spark-ignited engines. Habibi's results are for the 7-mode Federal-Test Cycle. These results are summarized as follows:

1. Lead particulate emissions are deposited along the length of the exhaust system. In addition, burned lead can be found deposited on engine parts and retained in the oil.
2. During high speed or high load driving conditions (such as acceleration) these deposits can be reentrained by the high velocity exhaust gases.
3. There is a general increase in lead emissions with mileage accumulation. The effect of accumulated mileage on emission rates and MMED of emitted particles is shown in Table 1 (Habibi - 1970, 1973). In essence, average particle size on a mass basis increases as the age of the exhaust system (mileage accumulation) increases.
4. Chemically, the very large particles ($>200\mu$) are 60-65% lead, 30-35% Fe_2O_3 and 2-3% soot. Again these results of Habibi are summarized in Table 1.

2.0 Rate of Removal of Lead Particulate Emissions

From the foregoing discussion of factors which influence the rate and character of lead particulate emissions, the following observation can be made:

- A. For city-type driving, which involves low-speed cruise, acceleration, deceleration and idle driving conditions, the production and emission of particles with MMED's greater than 5 microns is favored. Because of their mass and size, they will settle out from the atmosphere at a short distance from the tailpipe. Chemically, these particles will be composed mainly of $PbBrCl$ which is preferentially deposited on the outer shell of the particle.
- B. For turnpike driving which will be more of a higher constant speed type of driving, the rate of particulate lead emissions will be higher than for lower speeds, but the MMED particle size will be 1-2 microns, and chemically the lead salt will be $PbBrCl$ which is deposited on the particle surface.

Therefore, city-type driving produces more rapidly settling material and turnpike driving produces more aerosol-size material. The MMED of the particles increases with age of the engine-exhaust system for 7-mode driving cycles and the larger size particles contain a higher percentage of lead salts than do the smaller size (aerosol size) material. These properties have a very great influence on how lead particulate emissions will be partitioned between air, water, and solid phases both as function of time and as a function of the processes which describe the transport and transformation of these particles.

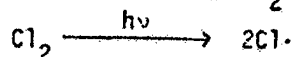
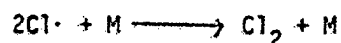
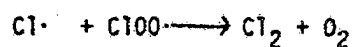
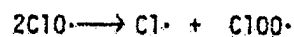
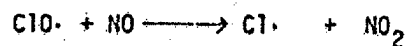
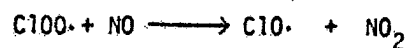
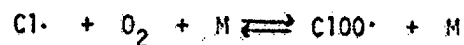
2.1 Rate of Removal of Aerosol-Size Lead Particulate Emissions

Aerosol-size lead particulate emissions have an MMED less than 0.5 microns. It has been adequately demonstrated that this material can be transported in the atmosphere for great distances (Huntzicker, et al. - 1975). In 1968, the average annual concentration of lead in air ranged from 1 to 4 $\mu\text{g Pb/m}^3$ (NAS-1972). In non-urban areas near cities, the average air concentration has been measured at 0.21 $\mu\text{g Pb/m}^3$, and for rural areas, the average air concentration has been measured as 0.10 $\mu\text{g Pb/m}^3$ (McMullen, et al. - 1970). Colucci, et al. (1969) found an annual average air lead concentration of 8.9 $\mu\text{g/m}^3$ near a busy New York City highway and 11.3 $\mu\text{g Pb/m}^3$ near a busy Los Angeles highway. In the Los Angeles study, 18 $\mu\text{g Pb/m}^3$ was the maximum value measured.

Habibi (1970, 1973) and Hirschler and Gilbert (1964) have determined that aerosol-size lead particulate emissions (particles less than 0.5 MMED) are composed of the double salt, $2 \text{ PbBrCl} \cdot \text{NH}_4\text{Cl}$, and carbonaceous material. Because of the sampling procedure used by Habibi (1973), it has been suggested by Ganley and Springer (1974) that this salt forms in the atmosphere after leaving the tailpipe.

Pierrard (1969) has studied the photochemical decomposition of lead halides from automobile exhaust. Both lead chloride and lead bromide darken when exposed to light (Norris - 1895, Renz - 1921), presumably releasing free halogen. The release rates for bromine and chlorine from the photolysis of PbBrCl have been determined as $1.6 \times 10^{-6} \mu\text{mole}/(\text{cm}^2) \cdot (\text{sec}) \cdot \text{milliwatt}$ of radiant energy for bromine atoms) and $1.0 \times 10^{-6} \mu\text{mole}/(\text{cm}^2) \cdot (\text{sec}) \cdot \text{milliwatt}$ for Cl atoms. Bromine and chlorine atoms react with O_2 to produce the free radicals $\text{ClO}\cdot$ and $\text{BrO}\cdot$. These two radicals can

participate in those atmospheric reactions which perpetuate smog forming reactions as follows:



Other constituents of automobile exhaust emissions include olefins, aldehydes, and ketones. The presence of an active halogen could result in the rapid addition of this atom to these chemical species. The lead portion of this dismembered PbBrCl salt presumably reacts with O_2 to produce PbO . This would be the predominant reaction, but reaction with organic constituents present in polluted air cannot be ruled out.

Aerosol physics and the growth and removal of aerosol-size particles by atmospheric processes has been studied by Heisler, et al. (1972) and summarized by Seinfeld (1975). Chemical reactions, condensation and evaporation, coagulation, and sedimentation are all important atmospheric processes which not only determine how rapidly the particle will be removed from the atmosphere, but also can be used to identify the source of that particle by the chemical element balance proposed by Friedlander (1973).

In attempting to quantitate the amount of lead removed by convective transport, use can be made of the correlation between airborne lead and carbon monoxide (Colucci, et al. - 1969). Huntzicker, et al. (1975) have refined this concept. On the basis of simultaneous measurements of lead and CO with corrections for other sources of these two pollutants, they have determined a dimensionless weight ratio of Pb/CO, of $6.2 \pm 1.6 \times 10^{-4}$. For the Los Angeles Basin, they estimate that approximately 21% of the lead emitted by automobiles is removed by convective transport of aerosol size and vapor phase organic lead compounds. The measurement of vapor phase organic lead compounds has been reported by Purdue, et al. (1973) and by Snyder (1967). Since there are losses to the atmosphere of gasoline by vaporization, it is conceivable that a portion of this measured organic lead could be tetraethyl lead. This could be confirmed by a technique using high-temperature electron capture GC developed by Green (1968). In the atmosphere, TEL could react with O_3 or OH radicals and ultimately be oxidized to PbO , but there is no verification of this mechanism.

2.2 Rate of Removal of Lead Particulate Emissions Which Settle out at Short Distances from the End of the Tailpipe

The major focus of this discussion will be on lead particles which have an aerodynamic equivalent diameter of greater than 5 microns. Because of their size and shape, they will settle from the atmosphere at very short distances from the end of the tailpipe. These particles will be deposited on all solid surfaces, such as roadways, gutters, sidewalks, buildings soil, plants, etc. In short, large lead particulate emissions will settle out on any surface or any living thing within the immediate proximity of the roadway. Because urban children often play in the immediate vicinity of city streets and roadways, it is important to understand what factors influence the rate of removal of these particulate lead

emissions which are deposited on surfaces, plants, and people located near roadways.

Creason, et al. (1971) set up an experimental program to determine if automobile emissions were a source of atmospheric contamination by lead, and if these emissions were of respirable size or were deposited on the soil near the roadway. Dustfall and suspended particulate pollutants were collected at four sites in metropolitan Cincinnati, Ohio, for a three-month period from July-September, 1968. The collection points were located at 25 feet and 100 feet from the road, and the sites were chosen to represent various urbanization and industrial patterns. For the three-month period, total dustfall rates ranged from 4.7-13.3 g/m²·month at the 25 foot locations and from 3.4-18.6 g/m²·month for the 100 foot locations. Dustfall rates for lead at the 25 foot sites ranged from 17-48 mg Pb/m²·month, and ranged from 8-17 mg Pb/m²·month at the 100 foot sites. The concentration of lead at the 25 foot sites for the three months averaged 3743 µg/g and 2942 µg/g at the 100 foot site. Unfortunately, there was no correlation of these mass fluxes and concentrations with traffic volume. Angle et al. (1974) measured dustfall rates, air concentrations, soil concentrations, boot tray concentrations (surface between top of shoe sole platform and the body of the shoe), milk, house-dust, and water concentrations of lead for urban locations in Omaha, Nebraska. The air concentration of lead ranged from 0.63 to 0.29 µg Pb/m³; dustfall rate for lead was 33 mg/m²·month in the urban area and 3 mg/m²·month in the suburbs; soil lead concentrations ranged from 444-123 µg/g; boot tray lead concentrations ranged from 1000-283 µg/g; lead concentration in house-dust ranged from 572-147 µg/g; lead concentration in milk averaged less than 0.04 µg Pb/ml; and lead concentration in water was less than 0.01 µg/g. These exterior fallout values of lead concentration and mass fluxes provided a significant correlation with measured blood lead levels for a group of urban and suburban children, all well past the age of the pica problem.

2.2.1 Chemical Reactions Involving Lead Particle Emissions

Olson and Skogerboe (1975) collected samples from the top centimeter of soil at sites within 2 meters of heavily traveled streets and highways in Fort Collins and Denver, Colorado, Chicago, and a highway leading to a lead smelter in the New Lead Belt of Missouri. From the work of Habibi (1970, 1973), the major chemical form of large particulate emissions from spark-ignited engines has been determined to be $PbBrCl$. The major chemical form of lead found in soil and city street dust collected from curb and/or parking lot areas was $PbSO_4$. Olson and Skogerboe (1975) reasoned that $PbBrCl$ was converted to $PbSO_4$, presumably by reaction with SO_2 . There was no kinetic rate information given for this conversion process. $PbSO_4$ has a solubility in cold water of approximately 0.004 gm/100cc. This is a water solubility which is about two orders of magnitude lower than for $PbCl_2$ or $PbBr_2$. There was no information on the solubility of $PbBrCl$. In addition, Olson and Skogerboe (1975) found traces of PbO_2 and PbO in the Fort Collins samples. In the Denver, Chicago, and Fort Collins samples, however, the predominant chemical form of lead was $PbSO_4$.

2.2.2 Runoff in Water

Lead particulate emissions deposited on urban streets, curbs, and sidewalks will be washed away by precipitation and street cleaning operations. This run-off goes into storm sewers which empty into receiving waters. Assuming that lead in street dust is in the form of $PbSO_4$, the water insolubility of $PbSO_4$ will cause it to precipitate and become part of river, stream, and ocean sediments. It should be remembered that the rate of removal of lead particulate emissions by this mechanism is a strong function of the amount, severity, and form of precipitation, and the frequency and efficiency of urban street cleaning operations. Whereas the weather is not predictable, urban traffic density patterns have been

well established. Therefore, it is not inconceivable that lead concentrations in urban street, curb, and sidewalk dust will rise between precipitation and street cleaning episodes, and drop sharply following either of these incidents.

Once transported to sediments, remobilization, availability and uptake by aquatic organisms and the implications of the presence of lead in water and food supplies have been the subjects of much research. This is rather an extensive literature and one of the major forums for the presentation of this type of information on the geochemistry of lead has been the Trace Substances in Environmental Health Meeting held annually in Columbia, Missouri, since 1966. The NAS Report on Lead (1972) also contains an extensive summary of this literature.

This example of the chemical transformation of lead particulate emissions which settle in dust and dirt to $PbSO_4$, its subsequent transport into the aquatic environment and deposition in sediments, and its subsequent transport into aquatic organisms, is the major public health concern associated with the widespread release of trace metals such as lead to the environment. Metals may change valence and associated ligands, but the metal itself is still present. There are natural background levels of lead in the environment, however, what is being measured in the studies reported here are levels of lead compounds which are substantially above background levels. Because lead is believed to be a nonessential toxic element, this continual build-up is viewed with great concern.

2.2.3 Deposition on Soils and Plants and Uptake by Plants

The deposition of lead particulate emissions on soil, the concentrations of lead as a function of distance from the highway, and the levels taken up by plants also have received extensive experimental consideration. Swaine (1955) estimated the average lead content in the earth's crust of 16 ppm with a range of 26 to 200 ppm. Bowen (1966) estimated an average world-wide lead content in soils of 10 ppm, again with a range of 2 to 200 ppm. Lead particulate emissions deposited

on soil can be subjected to the following transport phenomena: chemical reaction, absorption, adsorption, solubilization, leaching, runoff, microbially mediated chemical transformation, uptake by plants, reentrainment by wind, removal by children playing in dirt, removal on shoes of people walking through the area, and other physical transport mechanisms.

Schuck and Locke (1970) as a result of studies with consumer crops suggested that particulate emissions from the combustions of leaded gasolines by motor vehicles produced a topical dust coating of which 50% could be washed off with water. In addition, lead was not taken up by these plants via their root system. Ter Haar (1970) concluded from the analysis of plants grown at different distances from highways that the main source of lead in crops was derived from the natural pool already available to the plant in the soil. With regard to absorption by plants of particulate lead emissions, a number of other studies (Dedolph, et al. - 1970; Motto, et al. - 1970; Motto - 1970) do not reach any definitive conclusions. The suggestion, however, that particulate lead emission are simply deposited as a washable layer on plants is the general opinion of these authors.

Unpublished results for soils amended with radio-labeled $^{210}\text{Pb}(\text{NO}_3)_2$ (Battelle-Northwest - 1972) have shown that this soluble form of lead is not readily taken up by either barley or soybeans. Simultaneously, an analysis of the effect on soil microbial populations was undertaken for soils amended with 1, 10, and 100 $\mu\text{g Pb/gm dry weight of soil}$. These studies were designed to examine the mechanisms by which microbially mediated processes make metals more available for transport across root membranes and translocation within the plant. The natural lead concentration of the soil before amendment was 5 $\mu\text{g/g}$. Therefore, these additions represented substantial increases in the total quantities of lead in the soil.

The soil was classified as a Ritzville soil. At the three levels of lead amendments used, there were no observed effects on microbial numbers or respiratory activity. In addition, there was very little reduction in crop yields as soil amendments of lead increased. In effect, these studies confirm the observations that the plants normally exclude all but a very small amount of lead by a mechanism operating at the soil-root interface. For further discussion on the uptake of lead by plants, the reader is referred to the NAS Publication entitled Airborne Lead in Perspective (1972).

Beyond the recognition that lead particulate emissions can be reentrained during high wind meteorological conditions, not much more can be said about this removal mechanism. Runoff has been discussed earlier.

Observations by Lepow, et al. (1975) of the "mouthing" behavior of ten children who had been playing in an area where the average soil lead concentration was 11,000 $\mu\text{g/g}$, and the average lead concentration on the hands was 2400 $\mu\text{g/g}$, established that this was a significant mechanism for children to remove by ingestion, lead deposited on the soil. Similarly, Vosla?, et al. (1974) observed that the ingestion of housedust containing large concentrations of lead which was on the hands of children, was a source of a substantial intake of lead by children.

3.0 Rate of Accumulation of Particulate Lead Emissions

The final component in this pseudo-mass balance approach to how particulate lead emissions partition themselves between air, water, and solid phases of the environment, is a term describing the rate of accumulation of lead within a geographical area. It is apparent that both the time-scale and the location of the measurement site become very important factors for determining what the rate of accumulation will be. It follows from this, that at sites within a geographical area that the time dependent concentration would be either cyclic

or remain relatively constant. Measurement sites near a roadway will exhibit a cyclic type of behavior, whereas sites further from the road, but not near houses or buildings on which lead paints have been used, will exhibit a more nearly constant lead concentration as a function of time. The cyclic behavior of lead concentrations measured near the roadway is due to the inability of the paved surfaces to sorb lead particulate fallout. Precipitation, turbulent winds created by traffic, and street cleaning can cause the concentration of lead near a roadway to fall sharply. Even though the lead concentration fluctuates at sites near the road, it will always have a value greater than the concentration of lead determined at sites away from the road.

Concentration gradients for a perpendicular direction from a roadway and average concentrations of lead at locations in urban and rural areas have been determined by many authors. These concentrations and concentration gradients are point values which have been determined for a specific time, and may or may not represent the time dependent characteristics of lead concentrations for a particular geographic area. In order to understand the difference between the instantaneous value of the concentration and fluctuating nature of the lead concentrations, use is being made of the methods used to analyze the situation occurring in turbulent diffusion. The instantaneous concentration of lead is composed of a fluctuating concentration and a time-smoothed concentration.

Daines, et al. (1970) present data on atmospheric lead levels as a function of traffic volume and distance for the roadway. Dedolph, et al. (1970) have determined soil concentrations for lead as a function of distance from a roadway carrying an average vehicle load of 29,000 vehicle/day. They derive an expression for mapping soil lead concentrations at different location sites

from the roadway. Kinard, et al. (1975) have measured lead concentration patterns in soil for an urban setting in Columbia, S. C. A city block with variable vehicle loads on the streets in this area was used in this study. Hemphill, et al. (1974) determined lead concentration gradients in soil for a perpendicular direction from a roadway in Missouri which was used to haul lead ore to a smelter. Ter Haar and Aronow (1974) present concentration profiles for lead in soil for the perpendicular distance both from a road to a house painted with lead paint, and from a road to a brick house. As the house painted with lead-based paint was approached, the soil concentration dropped then rose to approximately twice the concentration of lead measured at or near the roadway. For the brick house, the lead concentration of lead measured at or near the roadway. For the brick house, the lead concentration declined until a position half way between the road and the street was reached. The concentration then increased as the brick house was approached, but did not reach the average concentration measured near the road. Day, et al. (1975) measured concentrations of lead in street dust at different locations in London. The concentrations of lead in dust ranged from 800-1500 ppm.

In summary, at or near the roadway, the lead concentrations in dust and dirt ranged from 700-4000 ppm. The upper value of 4000 ppm was from the study of Creason, et al. (1971). At a distance of 50 to 100 feet from the road, measured soil concentrations in different urban and rural settings gave values which ranged from 60-3200 ppm. In interpreting these results, care should be exercised since the type of buildings and the types of exterior finishes applied to these buildings are important considerations. In the air, lead concentrations ranged from 2.5-12 $\mu\text{g Pb/m}^3$ near the roadway to 1-2 $\mu\text{g Pb/m}^3$ at distances 100-500 feet from the roadway. Near the roadway, both air and soil concentrations of lead were strong functions of traffic volume or traffic load.

Even though the measurements on concentrations of lead in dust and dirt are made at specific times, the data of Creason, et al. (1971) do show definite changes in lead concentrations as a function of time. Therefore, these results and others cited, strongly suggest that there is a definite pattern of accumulation of lead in the environment from automobile exhaust and, that the measured concentrations are not just isolated measurements without significance. It should be remembered that this is a time-smoothed accumulation of automotive emitted lead or a residual concentration of lead remaining after the action of those rate processes which tend to remove lead particulate emissions from a given area, have been subtracted from the exhaust emission rate process for lead particulate matter which puts this material into this same area. Therefore, on a short-term basis, i.e. in between rainstorms, there will be positive accumulations of lead at locations near roadways. For urban children playing in areas near roadways, this short-term or fluctuating accumulation of lead in dust and dirt can present a significant exposure situation. On the basis of literature information reviewed, in urban environments the majority of lead emissions produced by city type of driving are large particles which settle out at short distances from the end of the tailpipe. The basic chemical form of this particulate emission is $PbClBr$ which is converted to $PbSO_4$.

TABLE 1

PHYSICAL-CHEMICAL CHARACTERISTICS OF PARTICULATE EMISSIONS FOR DIFFERENT ENGINES,
DIFFERENT FUEL LEAD CONTENT, AND DIFFERENT MODES OF DRIVING

Engine	Operating Condition	Fuel Composition	Total Emission Rate, gm/mile	PMED microns	Chemical Composition of Particulate Emissions	Reference
1954 Chevrolet 6 cyl	30 mph cruise	Not specified	0.15	Not given	At 30 mph, the average Pb content by wt. was 50%, Fe ₂ O ₃ content by wt. was 1%. At 50 mph, the average Pb content by wt. was 90%, Fe ₂ O ₃ content by wt. was 10%. Chemically lead was in the form PbBrCl·NH ₄ Cl	McKee and McMahon (1960)
1954 Oldsmobile V-8	50 mph cruise		0.15			
1954 Plymouth 6 cyl	30 mph cruise		0.04			
1954 Oldsmobile V-8	50 mph cruise		0.1			
1957 Chrysler V-8	30 mph cruise		0.06			
1957 Ford V-8	50 mph cruise		0.23			
	30 mph cruise		0.08			
	50 mph cruise		0.03			
	30 mph cruise		0.06			
	50 mph cruise		0.49			
	30 mph cruise		0.1			
	50 mph cruise		0.14			
A. Various 1966 Models; Average Deposit mileage 51,000	7-mode Federal Test Cycle 4 cold starts 4 hot starts	Leaded Fuel	0.51 0.24	Not given	Lead in particulate as PbBrCl; Pb content of particulate emissions ~ 17% by wt. Carbon content ~ 34% by wt.	Ter Haar et al (1972)
B. Various 1966 Models; Average Deposit mileage 30,000-50,000 mi.	7-mode Federal Test Cycle 4 cold starts 4 hot starts	Unleaded Fuel	0.32 0.13		Carbon content of particulate emission ~ 70% by wt.	
C. New cars 0-1,000 miles	7-mode FTC 4 cold 4 hot 4 cold 4 hot	Indolene + 3 ml TEL/gal. Indolene	0.20 0.12 0.22 0.11		Pb = 13% by wt., C = 47% by wt.	

D. Various 1963-1968 Models; Average Deposits 20,000-62,000 miles	25 mph cruise 45 mph cruise 60 mph cruise 7-mode FTC hot cycles cold cycles Full (35% cold, 65% hot) Acceleration (0-70 + 30-70)	Leaded Fuel	0.029 0.046 0.083 0.056 0.121 0.079	90% of Pb are fines <0.5 μ 1/3 coarse (<5 μ), 2/3 fines	Not given	
327 CID, V-8	Simulated Consumer Driving Cycle	3ml TEL/gal	0.4	@ 7500 mi. = 1.1 @ 16,500 mi. = 3.1 @ 21,500 mi. = 4.7	Not specified	Habibi (1970)
1969, 350 CID V-8	Simulated Consumer Driving Cycle	Leaded Fuel	0.4	@ 5000 mi. 1.1-2.1 by wt. is PbBrCl, 10% @ 16,000 mi. by wt. is PbBrCl-2PbO, 3.6-3.8 3% by wt. is PbSO ₄ on @ 21,000 mi. PbP ₂ O ₇ ; 33% by wt. is 4.7-5.7 C Particles 2-10 μ , PbBrCl @ 28,000 mi. is major constituent. >15 Particles <2 μ , 2 PbBrCl. NH ₄ Cl	Particles >200 μ : 50% by wt. is PbBrCl, 10% by wt. is PbBrCl-2PbO, 3% by wt. is PbSO ₄ on PbP ₂ O ₇ ; 33% by wt. is C Particles 2-10 μ , PbBrCl is major constituent. Particles <2 μ , 2 PbBrCl. NH ₄ Cl	Habibi (1970)
1969 Ford, V-8 310 CID	7-mode FTC Cold start after 10 cycles	Leaded Fuel	.51 0.27		Particulate emission composed of Pb, Br, Fe, and Zn	Ninomiya (1970)
1970 Chevrolet V-8	Steady, 2250 rpm (about 55 mph)	Indolene H0 0+3 ml TEL/gal Indolene H0 0+3 ml TEL/gal +1.0 theory EDB Indolene H0 30 (3ml) TEL/gal + motor mix scavenger Indolene H0 15 (1.5ml TEL/gal) Indolene H0 0	0.16 0.15 0.10 0.03 0.003	<< 0.1 0.65 0.10 1.5 --	For leaded fuels, particulate emissions composed of Pb, Br, Cl, and organics	Moran and Manary (1970)

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2. SENTINALS OF POTENTIAL LEAD HAZARD

1.0 "Normal", "Reference" and "Discrimination Values"

The term "normal blood level" and other "normal" values for body fluids or tissues with regard to lead hazard are frequently used. It is important that they not be abused in the context stated or implied. For this reason, a brief consideration of the use of the above terms in general appears to be in order, followed by the degree of its applicability to lead hazard.

"Normal value" is varyingly useful depending upon the degree of correlation of the values within and outside of the "normal range" with the clinical conditions involved. In some cases the correlation is good while in others it is not as good because of the following factors: transient, wide fluctuations in the values unassociated with clinical changes; insufficient specificity of the test for the parameter being tested and poor correlation between the value in the tested fluid and the degree of involvement of receptor sites either structurally, quantitatively or over time.

In addition, and equally as important, the term "normal" suffers in its use from three logical fallacies: ambiguity in context (i.e. it connotes healthy in the clinical sense; Gaussian in the statistical sense; and either ideal, conventional or habitual in the popular sense); the circular reasoning involved (i.e. a "normal" population is one which is, overall, free of a condition while the presence of differences from this group defines, overall, the presence of the condition); and emotional connotations attached (i.e. what is "normal" is acceptable while that which is "not normal", "abnormal", is harmful and should be corrected). For these reasons, while it would be surprising if "normal" were to be eliminated from use completely in the near

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future, an attempt is being made to foster the application of other terms introduced (1).

"Reference value" and "reference interval" are coming into greater use in Europe and North America. For example, 97° and 100°F (36.2° and 37.8°C) can be "reference values" for individuals or groups while this degree of variation would be indicative of an abnormal condition in others. Several "reference values" may be present for a test taking into consideration: the vitae of a reference population; external and internal conditions of specimen collection; the analytical method used with its associated precision and accuracy; and the statistical tests used.

The terms "discrimination value", "decisive value" and "critical value" are more specific. These are "the best dividing lines between the 'normal' and the 'diseased' or between 'those who need not be investigated further' and 'those who do'" (2). Sunderman (1) listed the factors for its determination: a clear definition of the disease; clear demarcation of the stage to be specified by the test; ability to detect a high proportion of "true positives"; ability to accurately eliminate other conditions (a low rate of "false positives"); knowledge of prevalence of the disease; and consideration of the risk to the patient of a positive or negative misdiagnosis. It is often not possible to get this degree of specificity with a single test. However, two or more tests can many times be used together to define the group of individuals that are "diseased" or that "need to be investigated further."

2.0 Whole Blood, Erythrocyte, Plasma and Serum Concentrations of Lead

"Normal values" for the concentrations of lead, mainly in whole blood, have been reported extensively. Obviously, all have not been determined with the same degree of precision and accuracy and much reference is made to variations between laboratories and on the same sample because of the trace concentrations often present and the ease of contamination at one point or another in collection or assay. Independent of the extraneous factors, however, it is more reasonable that a variety of "reference values" and "reference intervals" exist among groups of the infants, children and adults of both sexes, and in the varying populations and occupational groups assayed. It has even been sometimes stated, quite candidly, that the higher values in lead exposed groups are "normal" for the group.

In specifying only "normal values" as above, there is either the implication that the amounts present are of a nonhazardous nature or that there is an acceptable degree of hazard considering the circumstances. The ambiguity is that, for a particular individual or group, the value obtained may be outside of its "reference interval" and, under these conditions, the lead might be either safe or biologically hazardous at the present, or in the future because of accumulation or developmental aspects. These possibilities are not suggested by indicating a result as a "normal value" within the "normal range." "Reference values" and "discrimination values", where possible, would be more useful.

Waldron (3) recognized the above thoughts for lead hazard as follows. "A more valid approach would be for each center to establish its own reference values taking into account such factors as diurnal and seasonal variations (4-7) and then to match results against those for the appropriate reference

population. The results could then be expressed either in terms of standard deviations from the mean or as an age-race-sex specific percentile such as Elveback has described (8). Used in this way, blood lead estimations would alert the physician or environmental hygienist to an unrecognized source of contamination while at the same time serving as valuable corroborative evidence of excessive exposure in suspected cases of poisoning."

2.1 Whole Blood

Whole blood lead (Pb-B) concentration has probably been the most widely used test to detect human exposure to lead hazard. However, its diagnostic value at the border of the upper "normal" and the lower concentration levels for suspected exposure, is controversial. For example, easy contamination and poor quality of analysis in some laboratories have given spurious and widely divergent results (9-12). It has been found that whole blood lead is more a measure of very recent exposure (13-15) than of total burden, most of which is in both some of the hard and soft tissues. The lead in body stores, it is known, can be mobilized by chelating agents (16,17), and there is some data, by a variety of dietary and physiological factors (18,19). Dietary sources (food and beverage) and water, as well as paint, dust and dirt contamination (the latter group by hand to mouth or direct mouth transfer mainly by children) could cause transient fluctuations (20-24). The hematocrit is greater in children than adults, it can vary for a variety of clinical reasons and it is also decreased as a symptom of lead poisoning. On these bases, some have attempted correction of whole blood lead values for the hematocrit since the lead is mainly on and within the erythrocytes. The correction has been controversial (25-30). Finally, some hematologic effects occur in children and adults at blood lead concentrations below 40 $\mu\text{g}/100\text{ ml}$ (16,25,31-33). Between 50 and 80 $\mu\text{g}/100\text{ ml}$, chelatable lead

in children (34) and urinary excretion of two catecholamine metabolites in mice and in children and the brain concentrations of the compounds in mice (35), are affected. Also some clinical effects (3,36,37) have been reported in children and adults in this dose range.

Goldwater and Hoover (38) reported the "normal" concentrations of lead in blood and urine (150 ml of urine from a 24-hour collection) in over 800 specimens each from 16 countries, including New Guinea (aborigine population) and the United States. The subjects were mainly hospital employees or clinic patients, of both sexes, and were screened to eliminate cases of unusual exposure to lead. Chemically clean glass or polyethylene bottles were used for the samples which were mailed to a central laboratory in the United States for analysis by one of the standard dithizone methods.

They defined "normal", for the study, as "the amount found in persons who have had no evident occupational, medicinal, or other unusual sources of exposure." There is no implication of safety or hazard in the definition. The "normal" range found was about 5-40 $\mu\text{g}/100\text{ ml}^*$ and the values included those of 45, 50, 53, 60, and 100 (New York City) $\mu\text{g}/100\text{ ml}$ with, in all likelihood, additional values in the latter range. The distribution was skewed, as seen from the low median (18 $\mu\text{g}/100\text{ ml}$) and mean (17 $\mu\text{g}/100\text{ ml}$) values. In about 95%* of the tests the values were 40 $\mu\text{g}/100\text{ ml}^*$ or less.

*There seem to be three minor, but important errors in the Goldwater and Hoover (38) report. The derived, corrected values are given above and the justifications here. (1) From the data, it appears that the normal range of blood lead values is 5-40 rather than 15-40 $\mu\text{g}/100\text{ ml}$. (2) To be consistent with the paragraph directly above in their report and with the two values given in their Summary and Conclusions section, it appears that 95% of the blood lead values rather than 98% was meant. And then (3) the mean + two standard deviations would give about 40 $\mu\text{g}/100\text{ ml}$ rather than 50 $\mu\text{g}/100\text{ ml}$ as the value that includes 95% of the blood lead values; three standard deviations would yield 99% of all values up to 50 $\mu\text{g}/100\text{ ml}$. The interpretation of (3) is coherent with the paragraph above in their report where 95% of the urine lead values are included in two standard deviations (about 65 $\mu\text{g}/100\text{ ml}$). However, because the distributions are skewed, it can only be surmised that the corrected values are what was meant.

They referred to a comprehensive review of the world literature by G. J. Stopps, presented at a meeting (39) also referred to by Stopps (40), and reproduced partly elsewhere (41), which yielded similar and slightly higher values between 1941 and 1965 and some higher values, as well, between 1931 and 1940 (Figure 2.1). McLaughlin and Stopps (42) have now determined the blood and urine concentrations of lead, respectively, in 420 and 3,819 E.I. DuPont de Nemours & Co. employees, who were not working with lead products, at 23 locations in the United States and analyzed the data for nonsmokers vs smokers. The mean whole blood concentrations were: nonsmokers, 19.1 $\mu\text{g}/100\text{ ml}$; cigarette smokers, 19.9 $\mu\text{g}/100\text{ ml}$; other smokers, 17.3 $\mu\text{g}/100\text{ ml}$. These values were not significantly different. However, lead in the urine of nonsmokers was significantly slightly less than in the two other groups; 27.1 vs 28.6 and 29.0 $\mu\text{g}/100\text{ ml}$, respectively. They quoted several other studies that found a difference or no difference and, for two of these, gave the mean blood concentrations reported: nonsmokers, 16 and 16.3 $\mu\text{g}/100\text{ ml}$; smokers, 21 and 16.4 $\mu\text{g}/100\text{ ml}$.

Butt, et al. (43) reported a mean blood value for lead in 47 "presumably normal" hospital employees of 17.7 ± 0.8 (S.E.) $\mu\text{g}/100\text{ ml}$. They did not give the range and the standard error appears to be unusually small.

Robinson, et al. (44) reported data for children of ages 5 hours to 13 years, where there was "normal temperature...no history of pica, previous lead poisoning, or symptoms suggestive of lead poisoning". There were for 9 newborns: range, 7-28 $\mu\text{g}/100\text{ ml}$; for 28 infants including the newborns and up to 6 months old: range, 5-31 $\mu\text{g}/100\text{ ml}$ and median, 15 $\mu\text{g}/100\text{ ml}$; for 75 children from 6 months old to 13 years: range, 2-54 $\mu\text{g}/100\text{ ml}$ and median, 27 $\mu\text{g}/100\text{ ml}$ with 90% of the values from 15-40 $\mu\text{g}/100\text{ ml}$. The difference between the values for the newborn to 6 months and 6 months to 13 year groups was statistically highly significant. However, there was not a significant difference between groups from 6 months to 4 years and 4 years to 13 years, and thus, the 6 months to 13 year values were pooled for statistical analysis. All values were plotted on a scattergram.

2.2 Erythrocytes

Usually 90% or more of the blood lead travels with the erythrocytes (25,45) and the lead appears to be taken up rather quickly from plasma to erythrocytes (46,47); there appear to be easily and more difficultly released compartments for lead (18,47), one of which is associated with the membrane and the other inside the cell (48); inhibition of both heme (14) and globin (30) synthesis with their associated enzyme inhibitions and product accumulations occur (31), Na/K ATPase inhibition, K^+ loss and some degree of shrinkage and crenation (30) and fragility of the membrane (44,49) occur; and a decrease in the number of circulating erythrocytes (anemia) is often a symptom of lead toxicity (50).

The effects within erythrocytes and the spillover of accumulated products into the plasma and urine are objective factors and have been quantified. Some of these are seen at lower levels of lead exposure. They are reported further below. While the erythrocytes are considered by some to be mainly an inactive transport and storage site for lead, and while there is considerable evidence against at least the worst and most of the moderate of the following situations, several possibilities are either known to some degree or are still speculative. The following possibilities are not, by any means, implausible and should continue to be sought at the lower and moderate levels of blood lead concentrations.

(1) Some of the erythrocyte lead is easily releasable with chelating agents and may also be easily released to the plasma under a variety of dietary or physiological conditions, to be potentially available in the plasma for reaction with susceptible tissues; (2) direct effects on the erythrocytes may pose, in itself, some form of hazard; (3) effects on susceptible tissues, secondary to the erythrocyte responses may occur; and (4) some of the responses of erythrocytes may mimic types of events occurring at other sites.

2.3 Plasma and Serum

As noted above, most of the lead in blood is associated with the erythrocytes. In cases of increased total lead in blood or frank toxicity, what is the reported distribution of lead between the cells and the plasma or serum?

Among the earlier reports, Aub, et al. (51) reported that 80% of the lead in the blood of severely toxic rabbits was in the plasma. Teisinger (52) reported a more equal distribution between cells and plasma in human lead poisoning, but in a later report (53) stated that most of the lead was in the erythrocytes. Smith, et al. (54) reported the concentration of lead in serum in association with the development or disappearance of toxic symptoms in humans. After analyzing the extensive report by Smith, et al. more recent investigations on this issue will be reviewed.

Several factors must be noted at the outset in the Smith, et al. report: (1) In their extensive Tables, data for 45 of what appears to be 103 patients is presented in two or more Tables. (2) Lead exposure in 58 individuals (56%) was by the administration of a lead colloid, intravenously, for cancer chemotherapy. The other exposures were industrial, paint, unknown and X-ray exposure in one case (this type of exposure is unclear). The number of individual patients and their types of exposures are sorted in Table 2.1. Factors such as a potential altered distribution after i.v. treatment as compared to the inhalation and/or ingestion exposures, and the potential of an effect of the malignancy in those receiving lead colloid is considered here. (3) It is clear that Smith, et al. (54) were well aware that they wished to "minimize any changes in equilibrium of the serum and cell lead" from their description of the technique for defibrination and separation of serum from the clot, and its

justification. Bambach, et al. (45) presented data a few years later that the serum and plasma yield similar results for lead concentration under a variety of preparatory conditions. (4) The concentrations of lead have been converted from mg/10 ml to $\mu\text{g}/100\text{ ml}$; 10 $\mu\text{g}/100\text{ ml}$ was about the limit of detection. (5) The report is complex, the symptomology subjective in many cases and the interpretation of some parts open to differing opinions. However, there are important comparisons to be made with recent data. This report escaped quotation by many others partly, it is suspected, because few have measured plasma or serum lead concentrations in recent years, probably because these are generally considered to be quite low.

Some of the data are summarized in Tables 2.2 and 2.3. In Table 2.2 it is shown that there was no detectable lead in the serum of individuals of the authors' Tables 4, 5, and 11, representing respectively, "normals", individuals hospitalized for reasons not related to lead and patients mainly 4 months (2 months in one case) after a toxic episode. However, for the two groups of individuals of their Tables 9 and 10, who were either in acute toxicity or in an active phase of chronic toxicity, lead occurred in the serum. When the clinical symptoms were clearly present (their Table 9), the serum concentrations were 20-150 $\mu\text{g}/100\text{ ml}$, mean = 58 $\mu\text{g}/100\text{ ml}$; with weak or temporarily absent clinical symptoms (their Table 10), the serum concentrations were 10-40 $\mu\text{g}/100\text{ ml}$, mean = 20 $\mu\text{g}/100\text{ ml}$. The concentrations of lead in the cells + fibrin and in whole blood for the patients of their Tables 9, 10, and 11 were higher, as expected, than for the nonexposed individuals of their Tables 4 and 5.

Part of the data of their Table 12 is abstracted in Table 2.3 here. The concentrations occurring in serum from day 0 to as much as 150 days later is

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recorded along with the patients health status, relative to lead toxicity. Although there isn't a good quantitative relationship, the directions of change for serum lead concentration and the patient's clinical state are generally correlated.

There are little or no differences in mean serum concentrations when the lead colloid i.v., industrial, and unknown exposures are compared. Thus, for the clearly symptomatic patients, the concentrations were, respectively, 57, 69, and 48 $\mu\text{g}/100\text{ ml}$; for patients with weak or temporarily absent symptoms, these were 20, 18, and 20 $\mu\text{g}/100\text{ ml}$, respectively. There is a weak correlation between the serum and the cells + fibrin concentrations in the clearly symptomatic patients (their Table 9) but no correlation when there was little or no clinical symptoms (their Table 10).

Bessman and Layne (55) administered edathamil calcium disodium (CaNa_2EDTA) to two adults and three children and assayed either the whole blood or RBC lead concentration along with the plasma concentration for each, before and 2, 4, and 8 hours after treatment. The data are shown in Table 2.4. Prior to treatment, the blood or RBC lead was above normal in two cases, patients b and c, and the plasma concentration in c was quite high, 63 $\mu\text{g}/100\text{ ml}$. The treatment had variable effects on RBC lead, but increased the plasma concentration in each case, to a startling extent in patient c. No statement was made with regard to the clinical outcomes of the individuals.

Robinson, et al. (44) reported plasma lead concentrations for 82 "normal" children: in 53, lead could not be detected; in 22 it was $\leq 9\text{ }\mu\text{g}/100\text{ ml}$; and in 7 it was $> 9\text{ }\mu\text{g}/100\text{ ml}$ and hemolysis had occurred to some extent in apparently all of these.

Butt, et al. (43) reported serum lead concentrations in three groups of individuals in the Los Angeles area. In 122 blood donors, the mean serum concentration = 3.9 $\mu\text{g}/100 \text{ ml}$; for 96 hospitalized patients, the mean = 2.7 $\mu\text{g}/100 \text{ ml}$; and for 48 "normal" employees, the mean = 2.8 $\mu\text{g}/100 \text{ ml}$. Age, sex, auto driving, and length of time in the Los Angeles area did not appear to have an effect on the mean serum lead values.

McRoberts (49) published an interesting report on individuals working in an automobile battery factory prior to and following knowledge of this operation by the Factory Inspectorate. McRoberts became the appointed factory doctor. In the report he first reviewed, in depth, the basis for the belief that an increased plasma or serum concentration of lead might be associated with toxicity. Plasma, RBC, and whole blood lead concentrations were among the data collected for 18 individuals. Thirteen remained well, though some had an increased concentration of lead in the blood, and the other 5 had some forms of symptomology. The Tables in the report considered the 18 individuals separately.

Of the 13 individuals that remained well: plasma lead concentration on 29 blood samples was 1-10 $\mu\text{g}/100 \text{ ml}$ (plasma concentrations were not determined on hemolyzed samples); whole blood lead on 43 samples ranged from 33-173 $\mu\text{g}/100 \text{ ml}$ though values of 18 and 250 $\mu\text{g}/100 \text{ ml}$ were also obtained; and 5 of these 13 individuals had a transient anemia (hemoglobin $\leq 13.0 \text{ g}/100 \text{ ml}$; the lowest of the low hemoglobin values were 11.8, 11.9, and 12.3 $\text{g}/100 \text{ ml}$).

The first of five workers with the "symptoms" showed a slight tremor, occasional "stipple" cells, and a hemoglobin of 11.7 $\text{g}/100 \text{ ml}$. He had only

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been working in the plant for two weeks and there was no known previous occupational exposure to lead. The initial whole blood lead concentration was 510 $\mu\text{g}/100\text{ ml}$. It was 790 $\mu\text{g}/100\text{ ml}$ two weeks later, and then following suspension from work, the concentration was still high, after another month, at 535 $\mu\text{g}/100\text{ ml}$. The individual was hospitalized, though he was asymptomatic on examination by several physicians, at which time three weeks later, the plasma concentration = 16 $\mu\text{g}/100\text{ ml}$; whole blood = 313 $\mu\text{g}/100\text{ ml}$; and hemoglobin had risen to 14.0 g/100 ml by this time. The next day at 9 a.m., a sample showed plasma = 71 $\mu\text{g}/100\text{ ml}$; whole blood = 235 $\mu\text{g}/100\text{ ml}$. A small, test dose of calcium disodium EDTA was given i.v. between noon and 2 p.m. The 4:30 p.m. blood sample showed plasma = 59 $\mu\text{g}/100\text{ ml}$; whole blood 297 $\mu\text{g}/100\text{ ml}$. At 7:25 p.m. the individual had epileptic-type convulsions, frothing at the mouth, followed by cyanotic coma and temporary cardiac and respiratory arrest. Acidosis was present on blood analysis after resuscitation. At 9:30 a.m. the next day the lead concentrations were: plasma = 6 $\mu\text{g}/100\text{ ml}$; whole blood = 283 $\mu\text{g}/100\text{ ml}$; and the next day these were: plasma = 3 $\mu\text{g}/100\text{ ml}$; whole blood = 241 $\mu\text{g}/100\text{ ml}$. About a month later, discharged from the hospital, these were: plasma 10 $\mu\text{g}/100\text{ ml}$; whole blood, 141 $\mu\text{g}/100\text{ ml}$.

The second individual with "symptoms" developed anemia after three months with the firm. In the first four weeks of work suspension he complained of tiredness and intermittent, vague pains in the muscles of his arms and legs, though clinical examination didn't reveal abnormalities. Hematologic morphology improved with time. Hemoglobin was between 10.8 and 12.0 g/100 ml for about a month and then rose to 13.0 g/100 ml in another 1 1/2 months. Plasma lead concentration was from 3-8 $\mu\text{g}/100\text{ ml}$ over a five-week period, but with 22, 17, 16, and 12 $\mu\text{g}/100\text{ ml}$ concentrations interspersed, and only the 17 and 16 μg samples

seemed consecutive. Whole blood lead concentration varied from 66-120 $\mu\text{g}/100\text{ ml}$ in 14 samples, with a possible plateau between 106 and 120 $\mu\text{g}/100\text{ ml}$ within a ten-day period.

The third individual worked for seven days before suspension because of a hemoglobin of 11.2 g/100 ml. The anemia did not improve over a month, even with oral iron therapy. No other symptoms than this degree of anemia are mentioned. Plasma lead was 10, 15, and 4 $\mu\text{g}/100\text{ ml}$ on three samples, and the respective whole blood lead concentrations were 117, 66, and 22 $\mu\text{g}/100\text{ ml}$.

The fourth worker had been absent from work for a while because of "influenza". At the time of examination he complained of malaise, weakness, and general aches and pains. Two blood samples over a month's time, respectively, showed normal hemoglobin values of 15.2 and 14.9 g/100 ml; plasma lead concentrations of 16 and 5 $\mu\text{g}/100\text{ ml}$; and whole blood lead concentrations of 85 and 67 $\mu\text{g}/100\text{ ml}$.

The last worker complained of tiredness and irritability. His hemoglobin varied from 10.9 - 13.8 g/100 ml on seven samples over a four-month span, and in a seemingly cyclic pattern. Four of the blood samples in six (67%) from this individual hemolyzed to some extent. This was a high proportion since for only 3 of the 13 asymptomatic individuals, hemolysis occurred in 3 out of 5 (60%), 2 out of 5 (40%), and 3 out of 8 (37%) of the cases and there were few other instances of hemolysis. Plasma lead concentrations were 6 and 12 $\mu\text{g}/100\text{ ml}$, about three weeks apart, and respective whole blood lead concentrations were 415 and 480 $\mu\text{g}/100\text{ ml}$. Other whole blood lead concentrations for this individual were 88, 381, 435, and 480 $\mu\text{g}/100\text{ ml}$.

McRoberts concluded that 10 $\mu\text{g}/100\text{ ml}$ appeared to be an approximate dividing line between the presence and absence of symptoms, but that there was little correlation between concentration on a specific day and symptoms at that time.

Rosen, et al. (26) reported plasma lead concentrations and hematocrits for 165 children including: 13 newborns; 14 and 17 children in two "normal" whole blood lead range groups of 20-29 and 30-39 $\mu\text{g}/100\text{ ml}$ respectively; 8-24 children in succeeding 10 $\mu\text{g}/100\text{ ml}$ lead concentration ranges up to 90-99 $\mu\text{g}/100\text{ ml}$; 10 in the 100-136 $\mu\text{g}/100\text{ ml}$ range; and 17 children with sickle cell disease and with whole blood lead concentrations of 18-136 $\mu\text{g}/100\text{ ml}$. The plasma lead concentrations found in each case were somewhere between 1 and 7 $\mu\text{g}/100\text{ ml}$, with mean concentrations of 3.0-3.3 $\mu\text{g}/100\text{ ml}$. The mean hematocrit values were: 60% for the newborns; 36% for the two "normal" whole blood lead groups; 34% in the 40-49 and 50-59 $\mu\text{g}/100\text{ ml}$ groups; 33, 31, 29, 28, and 26%, successively, for the remaining groups; and 20% in the children with sickle cell disease. Thus, Rosen et al. demonstrated a remarkable constancy of plasma lead concentrations over a wide range of whole blood lead concentration and hematocrit values. Elsewhere, Rosen and Trinidad (18) discuss experiments with Ca^{++} and CaNa_2EDTA that decrease RBC concentrations of lead, and other factors (48,56-58) that also appear to affect this site of lead storage and, in some cases, also lead in bone stores. Chisholm (27) in an editorial to the Rosen, et al. (26) report, wisely points out that "whether plasma lead concentration is measureably higher in symptomatic (our underline) cases remains obscure", and indeed, Rosen, et al. do not state the clinical status of their children at any of the lead concentrations. It is not unusual, however, to see asymptomatic children in the presence of relatively high blood lead concentrations, but one might expect there to be some symptoms in this large number of children.

Angle and McIntire (25) found plasma lead concentration in the range of 4.5-7.2 $\mu\text{g}/100\text{ ml}$ in 40 teenagers, ages 14-18.

3.0 Enzyme Activity and Product Accumulation

3.1 General Principles

The use of biochemical analyses (some physiological and other function tests will also be mentioned), to aid in the diagnosis of illness is at least as old as the terms "physiological chemistry" and the field of clinical chemistry. Thus, the intermediates and end products of clinically important biochemical sequences, the activities of enzymes involved, incorporation of precursor molecules, concentrations of compounds along shunt sequences and the presence or concentrations of otherwise abnormal products have been used successfully to assess the degree and paths of tissue and organ pathology.

In more recent years, we have wished to precede the state of illness in a variety of ways, including: the detection of abnormally sensitive individuals and a description of the causes of sensitivity; the identification of populations at risk; assessment of lesser degrees of abnormal tissue and organ function to preclude treatment and to prevent irreversible deficits; and the identification of detrimental combinations of exposure, neither of which is as hazardous by itself.

As we learn more about what can be assayed and as the tests become more sensitive to smaller changes, not only do we learn about clinically relevant events but we enter the range of clinically, and perhaps even preclinically, insignificant changes. There are now both inappropriate sentinals and sentinals where a considerable difference of opinion can occur.

When we consider these differences of opinion we must recognize two types: the first is whether or not a change is actually of importance to the state of health; the other, whether or not this degree of change is to be accepted after balancing the benefits, risks, and actual detriments. The latter, however, is not the issue here. The question is rather, are the effects observed actually of preclinical or clinical significance?

Even here, two more subdivisions occur: has the change actually affected a clinically important sequence, or has the safety margin been reduced? And whether or not we will accept a reduction of safety margin is dependent upon a combination of the extent of margin that remains along with the nature of the risk, and an individual's psychological willingness to accept or not accept it. And to place the psychological aspect at the bottom of the system analysis is not, at all, to denigrate it, because it can enter in subtle ways at other stages, and also because we have learned considerably about how the mind and body interact in clinically important ways.

3.2 Clinical Sequelae of Lead Toxicity for: Lead Dose, Blood Concentration or Body Burden Comparison; and for Enzyme Activity or Intermediate or Product Accumulation Comparison.

The diagnosis of toxicity due to lead absorption has not been easy. It is made partly on the basis of subjective and objective symptoms, a variety of signs and a variety of blood or urine tests for lead, enzyme activities, and intermediate or endproduct accumulation, and if possible, by evidence of unusual exposure. Individuals may be asymptomatic or symptomatic and be in a variety of states of hazard. Goyer and Rhyne (59) point out that "the onset of lead toxicity, even acute toxicity, is not a sharply defined event. Rather, it

involves a continuum of change from normalcy to ill health (60)", and that "symptoms of toxicity or cellular effects of lead correlate with tissue content of diffusible or mobile lead....This concept explains at least in part why one individual with a relatively small exposure to lead and body burden of lead may have clinical symptoms of lead toxicity whereas a lead industry worker with large body stores of lead, largely in the form of fixed or nondiffusible lead in bone, may not have symptoms."

An individual who is in an asymptomatic phase can have an exacerbation of symptoms. Trigger mechanisms for this have been sought and may include normal physiological events, dietary influences, and chelation effects. Though these may act through the mobilization of stored lead, other mechanisms may also be operative.

3.2.1 Adults: Smith, et al. (54) ranked the symptoms and signs of lead toxicity in adults as shown in Table 2.5 with the caveat "It should be remembered that all of these symptoms will never be found in any single case and frequently a patient is presented for observation or treatment whose past history to lead exposure would cause one to expect symptoms conforming to Groups II or III when only those of Group I can be demonstrated." Lane, et al. (61) gave the listing as shown in Table 2.6, and Dagg, et al. (62), a shorter list of symptoms in descending order of their frequency as presenting symptoms (Table 2.7).

3.2.2 Children: The symptoms and signs in children are somewhat different than in the adult. For example, peripheral neuropathy is more common in adults than in children while encephalopathy is much more common in children (59). Irritability, vomiting, abdominal pain, ataxia, anorexia, behavioral changes, speech disturbance, seizures, intercurrent fever, and dehydration can be seen in

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children (16). Symptoms in children in descending order of frequency, as listed by Sachs, et al. (63), are shown in Table 2.8.

TABLE 2.1 SORTING OF INDIVIDUALS AND THEIR TYPES OF LEAD EXPOSURE

Smith et al. (54) Table No.	No. of unre- peated indi- viduals in the Table	No. of individuals for each exposure					No. of re- peated indi- viduals in the Table
		i.v. lead colloid	Indus- trial	Unknown	Paint	X-ray	
9	41	20	12	8	1	-	-
10	24	14	4	4	1	1	11
11	10	5	3	2	-	-	8
12	19	14	4	1	-	-	19
13	9	5	1	3	-	-	7
Total	103	58	24	18	2	1	

TABLE 2.2 LEAD CONCENTRATIONS IN SERUM, CELLS + FIBRIN AND WHOLE BLOOD OF FIVE CATEGORIES OF NORMAL AND LEAD-EXPOSED INDIVIDUALS

Smith et al (54) Table No.	No.; Types of Individuals	Concentration ($\mu\text{g}/100 \text{ ml}$)		
		Serum	Cells + Fibrin	Whole Blood
4	38; "normals"	Nil	10-110	10-50
5	47; hospitalized (nonlead)	Nil	20-130	10-60
9	41; acute and active phase of chronic toxicity with clearly pre- sent clinical symptoms	20-150 (mean= 58)	50-730	50-410
10	35; same as Table 9 but with weak or tem- porary absence of clinical symptoms	10-40 (mean= 20)	30-370*	20-180*
11	17; 4 months or more after an acute or active phase of chronic toxicity	Nil	140-640**	70-220**

*One of the 35 patients had concentrations of: 20 $\mu\text{g}/100 \text{ ml}$ (serum), 2,290 $\mu\text{g}/100 \text{ ml}$ (cells + fibrin) and 830 $\mu\text{g}/100 \text{ ml}$ (whole blood)

**An additional individual, the same as in the above footnote, and 2 months after the toxic episode had concentrations of: nil (serum), 1,110 $\mu\text{g}/100 \text{ ml}$ (cells + fibrin) and 640 $\mu\text{g}/100 \text{ ml}$ (whole blood).

TABLE 2.3 THE RELATIONSHIP BETWEEN CHANGE OF LEAD CONCENTRATION
IN SERUM AND CHANGE OF CLINICAL STATUS

Patient and Sequence of Serum Concentrations ($\mu\text{g}/100\text{ ml}$)	Sequence of Clinical Conditions
a* 20,60	Poor, died
b 30,20,nil	Poor, improved, well
c nil,20	Fair, symptoms after acidification therapy
d nil,40,50,nil	Good, fair, fair, well
e nil,30,20	Fair, poor, died
f nil,20,30,50,90,30,nil	Good, fair, worse, bad, bad, improved, well
g 10,50,nil	Good, fair, well
h 10,50,40,30,nil,nil,30,nil	Good, poor, improved, better, well, fair, poor, well
i nil,50,20,nil	Good, poor, improved, well
j nil,40,20	Good, fair, fair
k 10,20	Fair, fair
l 10,nil,nil	Fair, good, well
m 30,20,nil	Fair, good, good
n 30,50,nil,nil	Fair, poor, improved, well
o nil,30	Poor, died
p nil,20,20,50,50	Fair, fair, poor, poor, worse
q 30,nil,nil,nil	Fair, fair, good, well

*In the report (54) the patients are identified by initials, sex and type of lead exposure.

TABLE 2.4 EFFECT OF CaNa_2EDTA ON PLASMA, RBC AND WHOLE BLOOD LEAD CONCENTRATIONS

Patient	Age	Blood Fraction	Before Treatment	Hr after treatment		
			0	2	4	8
a*	Adult	RBC	15	-	23	3
		Plasma	2	-	17	19
b	Adult	Whole Blood	61	-	70	100
		Plasma	0	-	27	48
c	3 year	RBC	275	186	68	34
		Plasma	63	123	80	55
d	4 year	RBC	12	-	109	-
		Plasma	0	-	139	-
e	5 year	Whole Blood	7	12	10	12
		Plasma	2	22	17	12

*In the report (55), the individuals are identified by initials.

TABLE 2.5 CLINICAL SYMPTOMS AND SIGNS OF LEAD POISONING (54)

CHRONIC SYMPTOMS AND SIGNS OF LEAD POISONING	CHRONIC SYMPTOMS AND SIGNS OF LEAD POISONING PREGNANT	CHRONIC SYMPTOMS AND SIGNS OF LEAD POISONING PREGNANT
General symptoms		
Patient becomes easily fatigued, moody, restless and excitable	Fallor Anorexia Slight lead line Arthralgia Slight lassitude Fatigued easily Hypotension to 90 mm Slight pyrexia	Anorexia Irritation Lead line Arthralgia Jaunder General weakness Hypertension Pain in chest Wrist drop Foot drop
Digestive system		
Persistent metallic taste Slight anorexia Slight constipation	Metallic taste Coated tongue Anorexia Constipation Slight abdominal pain	Metallic taste Coated tongue Anorexia Marked constipation Drowsy and sick Nausea and vomiting Bilious abdomen Pain in chest
Nervous system		
Irritability Uncooperativeness	Slight frontal headache Slight tremors or Parin- sonian Syndr. Slight ataxia Insomnia Palpitation Increased reflexes Increased irritability Eye grounds may show choking of optic discs	Severe frontal headache Tremors Convulsion Ataxia Insomnia Convulsions Fibrillary twitchings Neuritis Visual disturbances Encephalitis Hemiplegia Coma Paralysis Cerebral palsy
Renal symptoms		
Lead which fluctuates between normal limits and a very slight rise	Trace of albumin and few granular casts in urine Lead which fluctuates be- tween normal limits and a positive rise	Toxic nephrosis Albuminuria Casts in urine Hematuria Hematuria Positive but fluctuating lead findings

TABLE 2.6 CLINICAL SYMPTOMS AND SIGNS OF LEAD POISONING IN ADULTS (61)

Mild symptoms and signs:

Tiredness, lassitude, constipation, slight abdominal discomfort or pain, anorexia, altered sleep, irritability, anemia, pallor, and less frequently diarrhea and nausea. The presence of a blue line in the gums and of a metallic taste are useful indicators of increased lead absorption.

Severe symptoms and signs:

Severe intermittent abdominal pain (colic), reduction of muscle power -- for example wrist drop, muscle tenderness, paresthesia, and other symptoms or signs of neuropathy or encephalopathy.

TABLE 2.7 CLINICAL SYMPTOMS OF LEAD POISONING IN ADULTS IN DESCENDING
ORDER OF FREQUENCY (62)

Abdominal pain
Constipation
Vomiting
Non-abdominal pain
Asthenia
Paresthesia
Psychological symptoms
Diarrhea

TABLE 2.8 CLINICAL SYMPTOMS OF LEAD POISONING IN CHILDREN IN DESCENDING
ORDER OF FREQUENCY (63)

Drowsiness
Irritability
Vomiting
Gastrointestinal symptoms
Ataxia
Stupor
Fatigue

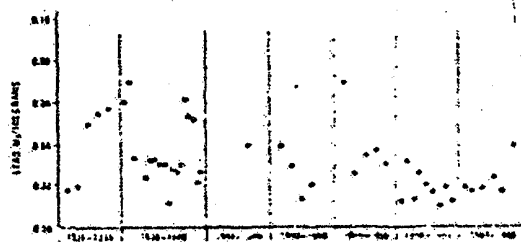


Figure 2.1 Lead Concentrations reported for "normal" populations, in five-year intervals, from 1931-1965 (41).

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3. RELATIONSHIP BETWEEN EXPOSURE TO LEAD AND HEALTH EFFECTS IN HUMANS

1.0 Introduction

In the United States the majority of non-industrial cases of lead intoxication occur in children between the ages of one and six years with the highest incidence between two and three years. Ingestion of lead-containing paint is considered to be the most frequent cause of severe lead intoxication among children. This may indeed be the etiology of the most severe poisoning cases; however, other sources of lead have assumed increasing importance. Recent clinical and experimental evidence has been gathered which indicate that important adverse health effects occur at levels of lead exposure that produce blood lead concentrations considered harmless in earlier years.

A number of cases of lead poisoning also occur in adults; many of these are either the result of occupational exposure to lead or are connected with consumption of illicit liquor. Contamination of foods with lead from ceramic dinnerware has produced fatal poisoning in children and adults.

The World Health Organization has established tolerable levels of intake of lead for adults (1972). These levels include lead from all sources.

Currently, no finalized guidelines exist on permissible levels of lead exposure for children which consider the metabolic differences between children and adults.

1.1 Variability of Response to Lead Exposure

Increasing levels of lead exposure generally are reflected by increasing concentrations of lead in whole blood. However, these are not precise relationships. Wide individual-to-individual variations exist between the concentrations

of lead in blood and development of specific symptoms of lead toxicity or between concentrations of lead in blood and in other tissues such as kidney or brain (Chisolm, 1971). The factors that precisely determine the partitioning between blood, bone, and such tissues as brain or kidney are not defined. However, as blood lead concentration increases, the frequency and severity of the manifestations of lead intoxication increase.

Zielhuis (1975a,b) recently reviewed the concepts of individual effects and group responses to a given dose of lead. He distinguished between the no-effect level, which is the maximum dose which does not result in an effect of particular intensity in an individual, with the response of a group as a whole with respect to a particular effect. Quantitative data available on effects produced by a known level of lead intake are individual data.

In determining a tolerable level of exposure to lead, it is important to have information relating duration and level of human exposure to lead with development of certain lead-induced biologic changes. Although large numbers of cases of lead poisoning have been documented in the United States during this century, data for use in determining dose-response and dose-effect relationships are scarce. Thus, none of the quantities discussed below are average values representing a large population; such values could differ substantially from the individual response data.

1.2 Metabolic Effects of Varying Levels of Lead Exposure

Although blood lead is not always a reliable indicator of the lead concentration in critical tissues such as brain or kidney, blood lead concentration has been used to express the body burden (Zielhuis, 1975a,b; Chisolm, et al., 1975a). Use of blood lead to equate body burden has some clear limitations.

Specifically, blood lead reflects only transport of lead to tissues, and due to equilibrium effects blood lead may remain constant while lead in such critical organs as brain and kidney increases.

There is considerable debate over the use of blood lead as an indicator of body burden in children. Chisolm, et al (1975b) recently reported that in children, erythrocyte protoporphyrin and urinary δ -aminolevulinic acid and coproporphyrin correlated well with urine excretion of lead following chelation therapy, while blood lead correlated less well with the chelatable lead.

Despite the limitations of blood lead concentration as an indicator of internal dose of lead, this measurement is utilized frequently because of the availability of blood samples. The Center for Disease Control (1975) recently established guidelines for the clinical evaluation of lead toxicity. Both blood lead levels and erythrocyte protoporphyrin determinations are proposed to assess metabolic effect and the degree of hazard. Determination of urinary excretion of intermediates of heme synthesis, such as δ -aminolevulinic acid requires 24-hour urine samples. It is very difficult to obtain urine collections for this length of time in young children and random urine samples are of little use in these analyses.

Tables 1 and 2 are presented in the Center for Disease Control Report (1975). Class I is "normal" with regard to lead, and it can have two subgroups as in Table 2: 1a, those children with iron-deficiency anemia, and 1b which, "on the basis of present available experience", indicates a "transient or declining blood lead elevation". For 1b, the significance for lead poisoning is downgraded because of the unaffected erythrocyte protoporphyrin (EP). Erythropoietic protoporphyria is distinguished from these.

Class II has two entries in Table 2. In both cases EP is minimally elevated. In one, blood lead is minimally elevated and in the other, lead is increased to the level of Class III. In the latter, however, the significance for lead poisoning is perhaps not as great because of the Class II finding of EP.

Class III has two entries. The significance of the one with the lower blood lead level is upgraded from what the lead analysis might suggest because of the moderately high EP value.

Class IV is considered to represent a high degree of hazard.

It is stated that "significant numbers of children with blood lead levels of 30-39 $\mu\text{g}/100\text{ ml}$ have shown evidence of metabolic impairment as detected by EP testing". The asterisks reflect combinations of lead and EP not generally observed.

Reigert and Whitlock (1976) studied 349 children and reported that "changes in FEP (free erythrocyte porphyrins) are slow and predictable whereas blood lead changes are quite unpredictable. However, when FEP suggests a different clinical category from blood lead, the blood lead is likely to change in the direction predicted by the FEP".

Benson, et al. (1976) described biochemical changes in men at weekly intervals, for up to 12 weeks after first starting work at a lead pigment factory. Blood lead began to rise within one week. After the first two weeks, three groups of response could be distinguished with regard to urinary δ -aminolevulinic acid and coproporphyrin excretion. In the first, an increase occurred after 3-4 weeks with variable increases afterward; in the second,

there were negligible changes; and in the third, there was an exaggerated response within two weeks of entry. The major finding, they say, was the very contrasting response shown by some individuals.

The following blood lead levels for the biologic effects indicated are found in Zielhuis' publications (1975a,b).

ALAD*: no-response level (no inhibition), about 10 $\mu\text{g}/100\text{ ml}$;
no-response level for >40% inhibition in adults, 15-20 $\mu\text{g}/100\text{ ml}$ and
in children, 5-10 $\mu\text{g}/100\text{ ml}$; for >70% inhibition in adults, 25-30 $\mu\text{g}/100\text{ ml}$
and in children, 20-25 $\mu\text{g}/100\text{ ml}$.

ALAU: no-response level for ALAU >5 mg/l, 30-40 $\mu\text{g}/100\text{ ml}$;
no-response level for ALAU >10 mg/l, 40-50 $\mu\text{g}/100\text{ ml}$. The levels
for CPU will be about the same; there are indications that in women
these levels may be lower.

PPE/FEP: no-response level in adult males, 25-30 $\mu\text{g}/100\text{ ml}$;
in adult females and children, 20-25 $\mu\text{g}/100\text{ ml}$.

Various other biochemical parameters: in most cases the no-
response level will be at least 50-60 $\mu\text{g}/100\text{ ml}$.

Hematologic effects: preliminary evidence is brought forward
that, at low blood lead levels, reduction of GSH and $\text{Na}^+ - \text{K}^+ - \text{ATPase}$
activity already may occur. However, the slope of the dose-response
curve is slight. If $\text{Na}^+ - \text{K}^+ - \text{ATPase}$ activity <40 $\mu\text{mole P/hr/mg}$ tyrosine
is taken as the specified response, the percentage of responses increases
already at $\text{PbB} = 20-29\text{ }\mu\text{g}/100\text{ ml}$, and for GSH <58 $\mu\text{g}/100\text{ ml}$ of RBC,

*ALAD = δ -aminolevulinic acid dehydrase in erythrocytes; ALAU = δ -aminolevulinic acid in urine; CPU = coproporphyrin in urine; PPE = protoporphyrin in erythrocytes; FEP = free erythrocyte prophyryns; GSH = glutathione; PbB = whole blood lead.

at PbB = 25-30 $\mu\text{g}/100\text{ ml}$. Anemia (decreased hemoglobin) does not occur in otherwise healthy adults below PbB = 70-80 $\mu\text{g}/100\text{ ml}$, and in socio-economically poor children not below PbB = 40-50 $\mu\text{g}/100\text{ ml}$.

2.0 Lead Exposure in Adults

2.1 Usual Exposure

Several estimates have been made of common levels of lead exposure. Because gastrointestinal absorption of lead by adult subjects is only about 5-10%, fecal excretion provides a rough estimate of intake. Kehoe (1961) reported "normal" mean 24-hour fecal excretions of $230 \pm 288\text{ }\mu\text{g}$ (S.D.) in a group of 453 subjects and $398 \pm 310\text{ }\mu\text{g}$ (S.D.) in 102 others. In the former group, the majority of persons had fecal lead excretions of less than 200 μg per day. Blood lead concentrations were not reported. The individuals were active adults, employed under conditions known to result in a negligible degree of exposure to, and adsorption of lead. The latter group was essentially similar. The difference in mean excretions was considered to reflect both local and individual dietary habits and the smaller sample size of the second group (Kehoe, 1961). Tepper reported that the average adult diet contains approximately 100 to 140 μg of lead per day (cited in King, 1971). Recent reports on dietary lead content (Kolbye, et al., 1974) indicate that the lead content of the diet of young adults generally averages from 150-250 μg per day.

2.2 Ingestion of Lead at Elevated Levels in Adults

Kehoe (1961) performed balance studies in four young, adult male volunteers. The period of study varied from several months to nine years. These men ingested lead as lead acetate or lead chloride along with their meals during

the test period, and the lead was added in quantities of 0.3, 1.0, 2.0, and 3.0 mg per day above normal dietary lead intake which was about 300 μ g per day.

Intake of a total of 0.6 mg of lead per day for one year resulted in a barely detectable increase in the lead content of urine and no demonstrable increase in blood lead concentration. The total 1.3 mg dose of lead per day resulted in a progressive increase in urinary excretion of lead and in the lead content of blood and other tissues. Persons ingesting 2.3 or 3.3 mg per day showed an increase in blood lead concentration which, if continued, would rise above 80 μ g/100 ml, a level that is generally believed to be hazardous. Kehoe (1961) also reported accidental exposure of two young adults who ingested between 5 and 10 mg of lead per day for one month. This level and duration of lead exposure produced symptoms of acute lead intoxication.

In the course of the balance studies, absorption of lead from the diet was found to vary between 5 and 10% for the young, adult male subjects. Similar results were reported by Hursh and Sumola (1968) using short-lived radioactive lead. Later workers, using stable isotopes of lead, determined lead absorption by adult males to be 6 to 14% of either lead nitrate or food lead when the lead was ingested with the meal. Under fasting conditions, gastrointestinal lead absorption can be as high as 70% (Rabinowitz, et al., 1974).

In 1974, Stulik reported the results of lead administration to adult (18-26 yr) volunteers of both sexes. Groups of five subjects received either 20 or 30 μ g Pb orally /kg body weight/day for three weeks, except on weekends.

The lead was given in a glycerin capsule after a meal. The body weights of the individuals were not reported. The following parameters of lead exposure were measured: whole blood lead, erythrocyte δ -aminolevulinic acid, and hemoglobin.

The responses and sequence of changes were as follows: at first, within three days, blood lead increased and erythrocyte δ -aminolevulinic acid dehydrase decreased. In females, erythrocyte protoporphyrin IX started to increase after about two weeks, up to two times pre-exposure values. In males ingesting 20 μg Pb/kg body weight, however, these changes were not observed. Males ingesting 30 μg Pb/kg body weight/day showed a small increase in erythrocyte protoporphyrin IX. Urinary δ -aminolevulinic acid increased transiently, only in the first week, in males at this dose.

Since the body weight of only one individual was given (125 kg), it is not possible to know the total dose of lead to the subjects. If a "reference man" is assumed to be 70 kg, the total dose at 20 μg Pb/kg body weight is 1.40 mg/day and, for a 54 kg "reference woman", 1.08 mg/day. At these levels of intake, blood lead concentrations rapidly increased in 7-22 days, from 20.6 to 40.9 $\mu\text{g}/100$ ml in males and from 12.7 to 30.4 $\mu\text{g}/100$ ml in females. The blood lead concentrations then tended to become constant. The subjects were treated with EDTA to remove accumulated lead.

At the higher dose, 30 μg Pb/kg body weight/day, the mean blood lead concentration rose to 46.2 $\mu\text{g}/100$ ml. It is not clear if these were the same volunteers of the first study. Blood lead in the female subjects reached 41.3 $\mu\text{g}/100$ ml, which is higher than the 30.4 μg Pb/100 ml produced by administration of lead, at the same dose, in the first experiment. These

differences may be due to individual differences if the subjects differed from the first experiment, or to changes in variables such as nutrient content of the diet, which is known to affect the percentage of lead absorbed. These results suggest that some differences exist between males and females regarding tolerance to lead. Females develop a significantly higher level of erythrocyte protoporphyrin IX than males at the same level of lead exposure. This study established that ingestion of approximately 1.0 and 1.5 mg of lead/day, for as short a time as 21 days, will result in significant increases in blood lead concentration and interference with heme synthesis (Stuik, 1974).

2.3 Inhalation of Lead by Adults

In adults, approximately 40% of inhaled lead is absorbed across the alveolar membrane or is absorbed by the gastrointestinal tract after being removed by ciliary action from the respiratory tract and swallowed (NAS, 1970). The amount retained will vary with particle size. The 40% figure is based on a "normal" mixture of particles occurring in urban air. Recently, Chamberlain et al. (1975) investigated the retention of ^{203}Pb by adults following inhalation. The source was exhaust from a combustion engine in which the fuel contained ^{203}Pb -tetraethyl lead. Thirty-five percent of inhaled lead was retained in the lungs and the lead was cleared from the lungs with a half-life of six hours. About half of the inhaled lead was present in the blood 50 hours after inhalation and about half of the ^{203}Pb was deposited in bone and in other tissues. From 72 hours on, the amount of ^{203}Pb in blood declined with a mean biologic half-life of 16 days. The investigators calculated that continuous exposure (24 hours/day) to a concentration of $1 \mu\text{g Pb/mm}^3$ of air, for a period of months, would result in an increase of $1 \mu\text{g Pb/100 ml}$ of whole blood.

3.0 Lead Exposure in Children

3.1 Lead Retention in Children

Experiments with children, similar to those performed in adults by Kehoe, have not been conducted. Closely controlled studies that provide information about the level of blood lead that accompanies a particular level of lead intake do not exist. Zielhuis' review relating blood lead concentration to hematologic and functional changes discusses mainly adults rather than children. The preponderance of clinical observations suggest that children develop symptoms at lower blood lead concentrations than adults. It is also highly probable that children develop a higher blood lead concentration at equal levels of exposure as compared to adults because of their greater rate of absorption and smaller body size.

Absorption of dietary lead by children has been reported (Alexander, et al., 1972) to be substantially higher than in adults. The children in this study were three weeks to eight years of age. A mean value of 50% net absorption and 18% retention of dietary lead occurred. Fomon, et al. (1976) conducted metabolic balance studies in young children from 2 to 25 months of age. Levels of lead ingestion higher than that usually in the diet were not investigated. A lead intake of less than 50 μg per day (based on individual balance data) appears to be accompanied by negative lead balance. Interpretation of the data at these levels is difficult and may be complicated by additional sources of lead than in food, water, and air, e.g. in dust and soil. For children, the actual percentage retention of inhaled lead is not known. Currently, as in the past, when calculations of lead exposure from

air for children are performed, adjustment is made for the smaller respiratory volume of children, but the same percentage retention is used as was determined experimentally for adults.

3.2 Estimates of Lead Exposure for Normal Children

Chisolm and Harrison (1956) determined mean fecal lead excretion of children aged 12 to 35 months with no known undue exposure to lead, to be 132 μg per day. The study of Barltrop and Killala (1967) of children 2 to 3 years of age and with no unusual exposure to lead, reported a mean fecal excretion of 130 μg per day with an upper normal limit of 180 μg . If one assumes that children absorb 40% of ingested lead, a fecal lead excretion of 130 $\mu\text{g/day}$ represents an average intake of 220 μg of lead per day from all sources. An average intake of dietary lead of 80 to 100 μg is suggested by the studies of Mahaffey (1976) and Kolbye, et al. (1974).

The Food and Drug Administration, under contract with the Comprehensive Health Care Clinics of Children's Hospital, Washington, D. C., determined dietary lead intake in self-selected diets of 1 to 4 year-old children (Mahaffey, 1976). The surveys were conducted in 1973-1974 and 1974-1975. In both surveys, the children selected were free of organic disease and were grouped as having a blood lead concentration of <30 or >40 $\mu\text{g Pb/100 ml}$ of whole blood. The groups were matched for age, sex, and other demographic factors. Average dietary lead intake was 105 μg per day in 1973-1974 and somewhat less, 80 $\mu\text{g/day}$, in 1974-1975. In neither survey was there a significant difference between the dietary lead intake of children with normal or elevated blood lead concentrations.

From available information on ingestion of lead, it appears that many 2 to 3 year-old children will tolerate an oral lead intake of up to 200 μg per day without an elevation of blood lead to $>40 \mu\text{g Pb}/100 \text{ ml}$ whole blood. Chisolm stated (cited in King, 1971) that as daily ingestion of lead is increased from 300 to 650 μg per day there is increased urinary excretion of δ -aminolevulinic acid, an adverse metabolic effect, i.e., interference with porphyrin metabolism, the formation of heme. This occurs as the blood lead concentrations rise above 40 $\mu\text{g Pb}/100 \text{ ml}$ of whole blood.

A joint FAO/WHO Committee (1972) established a provisional tolerable weekly intake of lead for adults of 3 mg but did not suggest a value for infants and young children. A Department of Health, Education, and Welfare-appointed ad hoc committee (experts in pediatric lead toxicity) recommended (King, 1971) that 300 μg of inorganic lead per day be the permissible amount from all sources for one to three-year old children. Mahaffey, et al. (1976b) estimated that young children are exposed to approximately 100 μg of lead per day from air, food, and water, but it is important to note that exposure for a particular child, on any given day, may be from 20 to 500% of this.

Although dietary intake of about 200 to 300 μg of lead per day appears to be tolerated by 2 to 3 year-old children, the acceptability of these levels for younger children and for infants of one year or less is not well established. Infants of less than one year are smaller in body size and have higher metabolic rates than 2 to 3 year-olds. These factors produce a proportionately higher exposure to lead from air, water, and food. In addition, calculations of tolerable lead exposure in proportion to body size may not be totally adequate

to establish tolerable lead intakes for infants as there are differences in maturation of the central nervous system, and young infants may absorb higher percentages of dietary lead than do two year-olds.

3.3 Estimates of Lead Exposure in Lead Poisoned Children

Chisolm and Harrison (1956) determined the 24-hour fecal excretion of lead by children under six years of age. The children were grouped on the basis of having blood lead concentrations of $<60 \mu\text{g}/100 \text{ ml}$ of whole blood, or $>60 \mu\text{g Pb}/100 \text{ ml}$ with or without symptoms of lead intoxication such as: anemia resistant to iron therapy, severe constipation, anorexia, hyper-irritability, bizarre behavior patterns, intermittent vomiting, accompanied by mild or severe encephalopathy.

Children who were found to be asymptomatic with blood lead concentrations greater than $60 \mu\text{g}/100 \text{ ml}$ had roentgenographic evidence of lead storage in bone and increased coproporphyrin excretion in the urine. The children with symptomatic lead poisoning excreted 5 to 104 mg of lead per day and the median value was 27 mg per day. Children with evidence of an elevated body burden of lead but without overt lead toxicity excreted between 116 μg and 9.6 mg per day with a median value of 1.1 mg per day. Those children with blood lead concentrations less than $60 \mu\text{g}/100 \text{ ml}$ of whole blood excreted between 12 and 175 μg per day. Chisolm and Harrison (1956) estimated that 5 to 6 months duration of exposures associated with these fecal lead excretions were required to produce these blood lead levels with or without the symptoms.

Barltrop and Killala (1967) reported fecal lead content of normal children and children with evidence of clinical lead toxicity from paint ingestion. Lead excretion was reported in mg per single fecal specimen which was collected

upon admission to the hospital or clinic. Normal children excreted a mean of 130 μg per specimen while the children with clinical lead poisoning excreted between 570 μg and 1.9 mg per specimen.

On the basis of these data, it has been concluded that absorption of 1 to 2 mg of lead daily for five to six months might cause symptomatic poisoning in 1 to 2 year-old children (Lin-Fu, 1972) or might cause an elevation of body burden of lead and a derangement of porphyrin metabolism (King, 1971).

Subsequent to these estimates of quantities of lead needed to produce symptomatic lead toxicity in children, three additional investigations on lead exposure in children have been reported (Ter Haar and Aronow, 1974a,b; Hammond, 1974). Ter Haar and Aronow (1974a) reported fecal lead excretion in $\mu\text{g Pb/g}$ dry weight of fecal material/day for 1 to 3 year-olds. Ten control children from suburban Detroit with no known exposure to an excess of lead excreted an average of 4 μg (range 2 to 7) /g dry weight/day, with a daily average of 15 g dry weight of fecal material. These values correspond to an average fecal lead excretion of about 60 $\mu\text{g Pb/day}$. Blood lead values for the control children were not reported in this publication. Eight children who had been hospitalized with the suspicion of elevated body burdens of lead excreted averages of 4, 7, 18, 19, 20, 40, 49, and 1640 $\mu\text{g/g}$ dry weight/day. For these children an average excretion is not very meaningful as two of them excreted lead in the control range, while one child excreted in excess of 1640 $\mu\text{g/g}$ dry weight/day. The total weight of fecal material excreted by the lead-exposed children was not reported. However, if daily

fecal excretion of 15 grams dry weight is assumed (however, see Hammond, 1974 below), the middle four concentrations correspond to an excretion of 270, 285, 300, and 600 $\mu\text{g Pb/day}$.

Thirty normal children (Ter Haar and Aronow, 1974b) from homes in suburban Detroit where lead poisoning was not a problem excreted a mean of 79 $\mu\text{g Pb/g dry weight/day}$ with a range of 22 to 174 and a median of 75 $\mu\text{g/g dry weight/day}$. Children thought to be exposed to lead excreted an average of 1781 $\mu\text{g Pb/g dry weight/day}$ with a range of 8 to 29,030 and a median value of 218 $\mu\text{g/g dry weight/day}$.

Hammond (1974) performed repeated determinations of fecal lead excretion by children having whole blood lead concentrations in excess of 40 $\mu\text{g/100 ml}$. He found that fecal lead excretion above "background" levels is highly variable, probably due to the fact that the pica habit that produces highly elevated fecal lead concentration is sporadic. He indicated that "by procuring several stool samples, a low lead sample is readily found in almost any child, irrespective of its blood lead concentration". However, the great majority of the children investigated by Hammond having blood concentrations of $>40 \mu\text{g Pb/100 ml}$ whole blood had fecal excretions of $>80 \mu\text{g Pb/g dry weight/day}$ with an average total dry weight of 6 g. The dry weight and lead content of fecal specimens in these studies were highly variable since constipation can occur in children with elevated body burdens of lead. Because of this variability, it is extremely difficult to estimate the quantities of lead ingested by children exposed to large amounts of lead on the basis of a single 24-hour stool specimen. It is not known if the absorption of lead varies with rate of passage of fecal material through the gastrointestinal tract. Background levels for children not exposed to elevated amounts of lead appear to be more constant.

4.0 Other Parameters Affecting Lead Toxicity

4.1 Form of Lead

Organic lead compounds such as tetraethyl or tetramethyl lead are highly toxic compared to inorganic lead compounds. Lead values on autopsy following tetraethyl or other organic lead poisoning are sparse. However, the partitioning of lead in the tissues in tetraethyl lead poisoning occurs as one would expect. Tetraethyl lead is lipid soluble and readily diffusible, resulting in rapid accumulation in nonosseous tissues, particularly the brain, and there is a rapid onset of symptoms. There is little time for lead to accumulate in bone before the symptoms of toxicity occur. This difference in partitioning of lead between persons dying of organic lead intoxication and those with chronic inorganic lead poisoning emphasizes the importance of the concentration of lead in a target organ rather than the total body burden of lead.

Data on the relative toxicity of different forms of inorganic lead show a much less clear-cut picture. Several points do stand out:

- (1) The solubility of the compounds in acidic or basic solutions is not, in itself, predictive of bioavailability.
- (2) Size is important. The same dose of lead as small particles is associated with greater lead absorption than with large particles. However, when large pieces of lead are ingested, as with lead shot or with a lead curtain weight, these may lodge in the gastrointestinal tract, slowly dissolve, and cause severe lead poisoning.

Part of the difficulty in interpreting data on bioavailability of different lead compounds is attributed to the variety of assay systems utilized. In long-term studies, the results have been reported from a number of species including ruminants and birds. The gastrointestinal systems of these species are markedly different from that of the human. A considerable amount of data has been obtained from studies in which the lead compounds were fed for 48 hours (Barltrop and Meek, 1975; Barltrop and Khoo, 1975). Although these studies were well controlled, their short duration provides information on only some aspects of lead absorption. Under circumstances where a difference in absorption may be due to physiological adaptation and not to the physical form of a compound, 48-hour studies are unlikely to detect these changes. For example, studies in animals have shown that iron deficiency enhances lead retention several fold (Mahaffey-Six and Goyer, 1972); however, this effect is not detectable in the short-term assay (Barltrop, personal communication). Barltrop (1974) reported that lead chromate, lead sulfide, and lead molybdate produced lower blood, kidney, and femur lead concentrations than did lead acetate, while lead oxalate and basic lead carbonate produced higher tissue concentrations of the lead. In these studies, the rats were fed diets containing the various compounds at equivalent lead levels for 48 hours. Elemental lead having a particle size of 180 to 250 μ was taken up only one-fifth as well as lead acetate. However, when particle size of the elemental lead was reduced to <180 μ , the tissue lead concentrations were approximately twice those with the larger particles. While considering particle size of importance, Barltrop (1974) noted that it is not possible

to predict particle size of added lead compounds after incorporation into the diet, or to predict the physical behavior of the particles in the lumen of the gastrointestinal tract.

Allcroft (1951) reported that 200 to 400 mg of lead/kg body weight, ingested in any one day as either the acetate, basic carbonate, or oxide, caused death of calves up to four months old. The apparent absorption of lead in sheep was reported (Blaxter, 1950) to be similar when the lead was given as the acetate, nitrate, or as naturally contaminated hay. However, because both the cattle and sheep are ruminants and have far different gastrointestinal systems than humans, these results are not necessarily predictive for human absorption of the compounds. Interestingly, Buck (1970) observed that lead in greases and oils is more toxic than elemental lead or lead salts. These differences could be due to the nature of the vehicle. Barltrop (1974) reported for rats that increasing the amount of corn oil in the diet increased the absorption of lead.

In ten-week studies, Ku et al. (1976) found that for both young and mature rats, ingestion of either lead acetate or a complex of lead with a phospholipid resulted in similar concentrations of lead in the femur, kidney, liver, and brain.

Several studies compared the bioavailability of lead as it occurs in natural foods with that of lead acetate. Equal concentrations of tissue lead were obtained in rats (Castles, 1976) and quail (Stone et al., 1976) fed oysters containing high concentrations of lead or an equivalent amount of lead as lead acetate either with or without the oysters. In both of these

experiments the trace metal contents of the diets were found to be constant in the diets. In humans, Rabinowitz, et al. (1975) found that blood lead concentration was the same when lead was that of the food or lead nitrate, when the total lead intake remained the same.

4.2 Presence of Other Components in the Diet

In general, it is not possible with certainty to separate effects produced by nutritional factors into a component that affects absorption of lead in the gastrointestinal tract from one that alters the metabolic capacity of the animal or human.

Garber and Wei (1974) investigated gastrointestinal absorption of lead in adult mice after oral ^{210}Pb acetate. They found that over a 1000-fold range of dose, the percent absorption of lead did not vary when food was withheld. Food in the gastrointestinal tract reduced the absorption of trace amounts of lead (0.02%) but did not affect the absorption of 2 or 20 mg Pb/kg body weight. The three chelating agents, ethylenediamine tetracetic acid (EDTA), diethylenetriamine pentaacetic acid (DPTA), and nitrilotriacetic acid (NTA), had variable influences. Neither EDTA nor DPTA altered lead absorption while NTA increased its absorption. In longer term studies in rats (7 weeks) Mahaffey and Goyer (1972) did not observe an increase of tissue lead when NTA was fed with the lead.

Regarding natural food components, Garber and Wei (1974) reported that lead absorption was increased by the chelating agent sodium citrate and by orange juice, which contains citric acid. Administering sodium citrate with HCl at a concentration similar to the acidity of the orange juice did not change the absorption of the lead.

For some time, milk has been considered to be an antidote for lead in cases of industrial poisoning. Data in experimental animals appear to be contradictory. Kello and Kostial (1973) gave six week-old rats a single oral or intraperitoneal dose of ^{203}Pb in trace amounts and reported large increases in lead retention when the diet contained several types of milk as compared to rat chow. However, Garber and Wei (1974) gave ^{210}Pb orally with larger amounts of lead as carrier to six week-old mice and found no effect of the milk on absorption.

It is not known whether the reported differences in the effect of milk on lead absorption are due to species variability, the dose of lead administered or other experimental variables. There is little doubt that diets supplying adequate amounts of milk can influence susceptibility to lead toxicity by means of providing an adequate supply of calcium and phosphorus. Less than adequate intake of these nutrients are known to increase susceptibility to lead toxicity in humans and experimental animals. Barltrop and Khoo (1975), while they did not test milk, itself, tested several milk components for an effect on lead absorption in rats. They found that the high fat and protein content of milk might be expected to increase lead absorption, but that this effect would be counteracted by the high mineral content of milk.

Other foods have been proposed for the prevention of lead poisoning. Several of these contain complex, relatively nondigestible carbohydrates. Carr et al. (1969) reported that in 7-8 week-old rats, when the standard laboratory diet contained 10% alginate, lead absorption was reduced. Kostial et al. (1971) reported that alginates reduced lead uptake from the gastrointestinal tract of newborn rats. However, in three human volunteers, additions

of alginate to the diet did not affect lead absorption (Harrison et al., 1969). Koshcheev et al. (1970) suggested that a generous supply of carrots and cabbage in the diet of workmen increased lead excretion and reduced urinary coproporphyrin III. The pectin and ascorbic acid contents of these products were considered to be the effective agents.

The overall ability of individual dietary components to increase or decrease lead absorption has not been established in humans. Studies to demonstrate these effects should ideally be conducted in humans over a relatively long period of time. The effect of foods would have a greater influence over a prolonged time rather than as short-term therapeutic measures. Alternately, animal testing would need to be done in a species such as the miniature pig, in which the gastrointestinal physiology is similar to that of humans.

4.3 Metabolic Condition of the Subject

There is a marked difference in lead absorption between children and adults. Details of the research defining these differences have been described above. Overall, young children absorb 3 to 10 times the amount of lead as do adults. Diets low in several nutrients appear to result in higher body burdens of lead at fixed levels of lead intake. For example, diets deficient in calcium and/or phosphorus result in higher tissue concentrations of lead at equivalent levels of lead intake. These effects of calcium and phosphorus have been reported for a number of animal species. Increased susceptibility to lead toxicity are not a direct function of level of calcium intake. When dietary calcium intake is below the physiological requirement for calcium, increased retention of lead occurs (Mahaffey et al., 1976a). Addition of high levels of calcium does not result in reduced retention of lead as compared

to retention occurring at normal levels of calcium intake (Mahaffey, 1976; Shields and Mitchell, 1941). On the basis of these observations, it is likely that a portion of the increased retention of lead is due to metabolic changes produced by calcium deficiency rather than simply the physical presence of calcium in the gastrointestinal tract. Increased absorption of lead has also been observed in balance studies with human infants receiving diets composed of normal infant foods. Slight reductions in dietary calcium content resulted in increased absorption of the lead present in these normal diets (Fomon et al., 1976). Effects of calcium at higher levels of lead ingestion are not known. Epidemiological studies with young children have shown that children with elevated blood lead concentrations consumed diets that were significantly lower in calcium and phosphorus than those of children with normal levels of blood lead (Mahaffey et al., 1976b).

Diets which are low in iron also increase retention of lead. A two- to three-fold increase in tissue lead retention of rats occurred on diets deficient in iron (Mahaffey-Six and Goyer, 1972). The degree of iron deficiency was not extreme as animals from this experiment showed only a modest decrease in hemoglobin concentration. Dietary deficiencies of iron commonly occur in the population groups in which lead poisoning is most frequent. Levander and co-workers (1975) reported that weight gain and hematocrit were significantly lower in vitamin E-deficient animals fed lead than in animals which were either only vitamin E-deficient or fed lead alone. Tissue lead concentrations are not reported in this publication. Sobel et al. (1938) reported that lead absorption as demonstrated by tissue lead concentrations is greater in rats receiving diets to which vitamin D was added than on rats receiving vitamin D deficient diets.

Deficiencies of nutrients do not always produce increased absorption of lead. For example, neither low nor highly elevated intake of ascorbic acid appreciably influenced tissue retention of lead (Mahaffey and Banks, 1975).

Factors other than minerals and vitamins have been found to influence lead absorption. Barltrop and Khoo (1975) reported that increasing the fat content of the diet resulted in a higher absorption of a dose of lead. The protein content of the diet is also a factor in determining susceptibility to lead toxicity. Baernstein and Grant (1942) found that rats fed lead chloride showed lower mortality and a diminished weight loss when the protein level of the diet was increased from 6 to 13 and 20%. Gontzea and co-workers (1964) observed that doubling the protein content of the diet from 9 to 18% in the rat decreased susceptibility to lead toxicity as judged by lead content of liver, kidney, and blood. Der et al. (1974) observed that rats fed 4% protein diets had higher blood lead concentrations than animals fed 20% protein diets when lead was injected subcutaneously. These data are difficult to interpret because both groups of rats were injected with 100 µg of lead acetate daily for 40 days. Rats receiving diets containing 4% protein were severely growth-retarded. With equal quantities injected, the dose per unit body weight was markedly different.

The pathologic effects of lead are more closely related to the concentration of lead in critical tissues such as brain and kidney than to total body burden of lead. A number of metabolic factors in the subject act to determine the amount of lead absorbed and the partitioning of lead between tissues such as brain and kidney and storage in a relatively nondiffusible matrix such as bone.

Table I

Test	Class I normal	Class II minimally elevated	Class III moderately elevated	Class IV extremely elevated
Pb	≤ 29	30-49	50-79	≥ 80
EP	≤ 59	60-109	110-189	≥ 190

Table II

Test results	EP ≤ 59	EP 60-109	EP 110-189	EP ≥ 190
Pb ≤ 29	I	Ia	Ia	EEP+
Pb 30-49	† Ib	II	† III	† IV
Pb 50-79	•	† II	III	† IV
Pb ≥ 80	•	•	•	IV

EEP+ = Erythropoietic protoporphyria.

• = Combination of results is not generally observed in practice; when blood lead is repeated, the results will generally indicate continuation of the first specimen.

† = Downgrading of the estimate of risk of lead intoxication suggested by blood lead is altered on the basis of the EP results.

† = Upgrading of the estimate of risk of lead intoxication suggested by blood lead is altered on the basis of the EP results.

CHAPTER 3

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1.0 Neurotoxicity of Lead1.1 Effects of Lead on the Central and Peripheral Nervous System1.1.1 Encephalopathy:

The neurotoxicity of lead at high levels of exposure has been well documented for both man and animal species. Acute encephalopathy is one of the most serious consequences of plumbism, since permanent impairment of the central nervous system may occur, particularly in young children. Byers and Lord (1943) showed that lead encephalopathy produced some irreversible neurological and psychological sequelae in 19 out of 20 children. The American Academy of Pediatrics (1969) estimates that 25% of children affected with lead encephalopathy will suffer permanent damage to the central nervous system. This damage is usually reflected in behavioral and educational abnormalities, with or without accompanying mental retardation. Perlestein and Attala (1966) observed that 82% of children with a history of lead encephalopathy experienced recurrent seizures and mental retardation. Mellins and Jenkins (1955) and Bradley and Baumgartner (1958) found that 60-80% of children treated for plumbism later had impaired visual-motor coordination. Smith (1963) found abnormal EEG tracings in six of ten children affected with encephalopathy. Children who have already experienced lead encephalopathy and are subsequently re-exposed to lead, will almost certainly develop permanent CNS damage (Chisholm and Harrison, 1956). Recently, Albert, et al. (1974) and Rummo (1974) have reconfirmed the detrimental effects of severe lead poisoning on the subsequent behavior and intellectual functioning of children.

1.1.2 Neurological Diseases:

Lead exposure has been linked to several chronic neurological diseases (Warren, 1974). Cone (1934) reported that the cerebrospinal fluid of

multiple sclerosis patients contained elevated lead levels; however, Butler (1952) and Westerman (1974) using more sensitive techniques for lead analysis were unable to show an association between lead absorption and multiple sclerosis. The possibility of an association has been revived by Warren (1963, 1967, 1974) by demonstrating that geographical areas with high environmental lead levels have a high incidence of multiple sclerosis.

A number of studies (Campbell, et al. 1970; Livesly and Sissons, 1968; Simpson, et al. 1964) have reported an association of exposure to lead with motor neuron disease, but the etiological role of lead is not clear in these studies. Lead insult has also been associated with scrapie and swayback in sheep, and kuru and amyotrophic lateral sclerosis in humans (see Warren, 1974). These suggestive associations warrant further investigation, but to date, controlled, positive studies are lacking.

1.1.3 Peripheral Neuropathy:

Animal studies have shown that lead produces segmental demyelination (Fullerton, 1966; Lampert and Schochet, 1968; Sauer, et al. 1970), and interferes with myelin metabolism in tissue culture (Cole and Lynam, 1972). Such damage to the myelin sheath has been shown to impair nerve function. Catton, et al. (1970) and Seppäläinen and Hernberg (1972), using sensitive electrophysiological techniques, observed impaired motor nerve conduction velocities in neurologically symptom-free lead workers, whose blood lead levels exceeded 70 $\mu\text{g}/100\text{ ml}$. Of particular importance are the more recent studies by Seppäläinen, et al. (1975) which revealed a slowing of motor conduction velocity of the median and ulnar nerves of asymptomatic workers whose blood lead values had never exceeded 70 $\mu\text{g}/100\text{ ml}$. Abnormal measurements

began to occur at blood lead levels of 50-60 $\mu\text{g}/100\text{ ml}$. These abnormalities were not as great as observed in the earlier heavily exposed workers. Thus a dose-response relationship appears to exist. No correlation between biochemical tests of exposure and neurological signs was observed. These preliminary findings do suggest that the acceptable level of blood lead (70 $\mu\text{g}/100\text{ ml}$) for occupationally exposed workers may need to be reevaluated.

Peripheral neuropathy has been considered to be a rare occurrence in children with lead intoxication (see Seto and Freedman, 1968). However, it is possible that childhood neuropathy is sometimes overlooked and overshadowed by the clinical symptoms of encephalopathy (Feldman, et al. 1973). These authors observed slightly reduced motor nerve conduction velocities in children with a known history of plumbism. Whether peripheral neuropathy occurs in asymptomatic children with no history of lead poisoning remains a matter of conjecture and is discussed in the following section.

1.2 Neurological and Behavioral Toxicity of Chronic Lead Exposure in Children:

A growing concern, which has received a great deal of publicity recently, is the possibility that chronic, asymptomatic lead exposure may cause "minimal brain dysfunction", behavior problems, and neurological impairment in children exposed to lead in utero and/or during early childhood. Wiener (1970) reviewed the literature up until 1968. He concluded that methodological shortcomings in all of the studies made it impossible to draw definitive conclusions.

Wiener notes that:

"Those reports which claimed positive findings had either used too few cases from which to generalize or had not provided for controls for relevant variables such as social class, pica; or premorbid status.

A rigorous statistical and experimental approach has been conspicuously absent. Further, the variations in diagnostic procedures and definitions lead to unclear conclusions regarding the degree of lead ingestion which may or may not be important for later development."

A brief critique of some representative, frequently-cited studies will indicate that such criticism continue to apply, in varying degrees, to all subsequent studies. For example, David, et al. (1972) suggested an association between lead exposure and hyperactivity in children. Children, whose hyperactivity had no known cause, had higher blood lead levels and body burdens of lead than normal children or children whose hyperactivity had a "known cause". However, since the numbers in the "known cause" group were very small, it cannot be ruled out that lead absorption was secondary to hyperactivity, particularly since it has been shown that disturbed children tend to exhibit an increased incidence of pica (Bicknell, 1967; Klein, et al. 1974; Cohen, et al., 1976). The statistical treatment of this study by David, et al. has also been criticized (Bulpitt, 1972).

Pueschel, et al. (1972) and de la Burde and Choate (1972, 1975) compared children with a history of pica and elevated blood lead levels (40 $\mu\text{g}/100\text{ ml}$ and above), to control children with no history of pica. The lead exposed children showed mental impairment, irritability, and poor fine motor control. In most cases, lead blood concentration was high ($>50\text{ }\mu\text{g}/100\text{ ml}$). Although the groups were matched for race, age, sex, and several socio-economic variables, no lead assessments were made for the control group. Again it can be argued that children with some history of psychological disturbance (i.e. pica) may have other signs of disturbance which are not directly related to lead exposure.

Kotok (1972) included pica in addition to age, sex, race, and environmental factors in matching his controls. He failed to find significant differences in mental development between lead exposed (blood lead $> 40 \mu\text{g}/100 \text{ ml}$) and control groups and concluded that the differences observed were related to home environment rather than lead exposure. However, his controls (many of them were siblings of the exposed group) had a mean blood lead of $38 \mu\text{g}/100 \text{ ml}$. Thus, as many of the controls may have been at high risk for lead, and Kotok's data must be considered inconclusive (Nieburg, 1972).

Other studies suggesting a causative association of lead exposure with mental impairment have been equally inconclusive (Perino and Ernhart, 1974; Rummo, 1974; Millar, et al. 1970; Baloh, et al. 1975; Beattie, et al. 1975).

The studies described up to this point have dealt primarily with urban children whose exposure to lead may come from many sources. Recently, attention has also focused on the effects of chronic lead exposure in children living in the vicinity of ore smelters (Roberts, et al., 1974; Whitworth, et al. 1974; Landrigan, et al. 1975b).

McNeil and Ptasnik (1974) evaluated 138 children (21 months - 18 years old) living in Smeltertown, Texas. Smeltertown is adjacent to a large ore smelter in operation for about eight years. Serial blood lead determinations indicated that these children had prolonged, asymptomatic elevations in blood lead levels ($40 - 80 \mu\text{g}/100 \text{ ml}$). They had no neurological symptoms, and nerve conduction tests were normal. The authors found no differences in the activity, measurements, and psychometric evaluations of exposed children and matched controls, living outside of Smeltertown. They concluded that sustained blood lead levels of $40-80 \mu\text{g}/100 \text{ ml}$ had not resulted in any apparent deleterious effects

Landrigan, et al. (1975a) evaluated the neuropsychological function of children living near an ore smelter in El Paso, Texas. They concluded that at blood lead levels of 40-80 $\mu\text{g}/100\text{ ml}$ subtle impairment of nonverbal cognitive and perceptual-motor skills occurred. However, since their controls were poorly matched with respect to age, history of pica, etc., the etiological role of lead cannot be clearly established.

Another study by Lansdown, et al. (1974) found no association between blood lead and intelligence and activity levels of school children living near a smelter. These authors concluded that social factors were more important than physical exposure to lead in determining mental development. However, their social factors were not quantified and very subjective assessments of behavior were used (Bryce-Smith, et al., Landrigan, et al., David, et al., 1974), thus rendering their conclusions dubious.

Neurological and psychological evaluations have also been made on a large, random sample of children living near a primary smelter in Shoshone County, Idaho (Shoshone Lead Health Project, 1976). Landrigan, et al. (1976) evaluating matched pairs of children (with 40 $\mu\text{g}/100\text{ ml}$ as the standard to divide the children into low and high blood levels) reported a significant correlation between lead intake and slowing of motor nerve conduction velocity. However, Gregory, et al. (1976) independently forming their own set of matched pairs (also using 40 $\mu\text{g}/100\text{ ml}$ as the standard delineating point), found no differences in nerve conduction velocities or intellectual measures between the lead exposed and control children.

Gartside and Panke (1976) have reviewed the matched pairing techniques and statistical analyses used in the Landrigan and Gregory studies. They also noted that in the Landrigan study only six children (out of 202) had nerve conduction velocities below the lower limit of normal children with similar ages (Gamstorp, 1963). When other matched pairing and statistical analyses were performed on the same two groups of children, no significant differences were observed. It should be noted that the use of 40 $\mu\text{g}/100\text{ ml}$ blood lead level to divide the pairs is arbitrary. Sets of matchings using different dividing points might produce different statistical results. Since conflicting results are produced using different ways to analyze the same data, a significant relationship between blood lead and nerve conduction velocity in children cannot be established.

The crux of the problem, applicable to all the studies cited, is that many of the traditional methodologies, approaches, and data analyses used to assess the behavioral and neuropsychological consequences of lead exposure in young children are open to subjective interpretations. For example, the assessment of "hyperactivity", a syndrome not well-defined operationally, often relies primarily on the "impressions" of parents and teachers. Baloh, et al. (1975) found that many mothers reported overactivity in children with elevated lead levels, but this was not observed in objective behavior ratings by a neurologist or psychologist. On the other hand, it is difficult to validly assess children's behavior outside of their every day environment. Matched controls cannot accommodate all the significant, concomitant variables

which may affect activity levels and mental functioning. A persistent reliance upon such traditional approaches will only succeed in stimulating controversy.

Another general criticism of these studies is that testing is performed primarily on school age children. These studies were unable to document whether excessive lead absorption, encephalopathy, etc. occurred in infancy and early childhood; i.e. during the time that suspected brain damage is most likely to occur. Young children's intelligence and behavior must be assessed before exposure to lead to determine whether an elevated lead burden causes or was caused by defects in mental abilities. Even then, other causative factors must also be considered. Thus the data presently available are inadequate to conclude that subtle psychological, emotional, and neurological sequelae occur as a result of lead exposure at levels below those causing clinical symptoms.

1.3 Behavioral Toxicity of Chronic Lead Exposure in Animal Species:

Table 4.1 summarizes some of the pertinent literature on the effects of pre-natal and neonatal lead exposure on the subsequent development and behavior of several animal species. Delayed nervous system development, deficits in visuo-motor functioning, abnormal social and aggressive behavior, hyperactivity, hypo-activity, and no changes in activity have all been reported. Parameters which measure central cognitive functions (learning, memory, etc.) do not appear to be generally affected. It is difficult to compare these studies, since the dosage, chemical form, route, timing of lead administration, and the technology used to assess the behavioral and psychological parameters vary considerably. Unwarranted generalizations and extrapolations from limited behavioral measures have frequently been made. A brief analysis of some of the more frequently-cited studies

indicates that the investigations on animal models have confused rather than clarified the human data.

Sibergeld and Goldberg (1973, 1974), exposed suckling mice to 1090-5500 ppm lead acetate through their mother's milk and at weaning directly through the drinking water. They reported a three-fold increase in their spontaneous locomotor activity as compared to control mice. Although lead toxicity symptoms were not apparent, the growth of the lead exposed offspring was significantly retarded, as indicated by reduced body weights and developmental delays. Thus the nutritional status of the animals was not adequately considered. Malnutrition confounded the early studies of Sauerhoff and Michaelson (1973) who also observed an increased spontaneous activity in the offspring of nursing rats exposed to 27,300 ppm lead acetate in the diet. In a subsequent study, Golter and Michaelson (1975) found that oral administration of lead acetate to suckling rats did not affect their growth rate, but that these rats continued to exhibit periods of increased motor activity. These investigators tested the activity of six siblings simultaneously without specifying the sexual composition of each litter. Since female-locomotor activity is known to vary with the stage of the estrous cycle, spurious activity measurements could have occurred in either their control or experimental groups. Exposing pups via the mother's milk may also add the confounding variable of possible maternal effects.

The more crucial issue, however, is that the doses of lead administered, resulted in malnourished offspring. Michaelson, et al. (1976) recently reported that early undernutrition, comparable to that frequently reported in lead-exposed mice, resulted in enhanced spontaneous locomotor activity. Castellano and Oliverio (1975) also reported that malnourishment can cause increased

extrapolatory activity and impaired avoidance behavior in mice. Sobotka, et al. (1974) found that malnourished weanling rats displayed a state of heightened 'emotionality' and impaired learning behavior. Thus some of the behavioral responses seen in lead exposed rodents may be due to early under-nutrition.

Reiter, et al. (1975, 1976) investigated possible effects of the nutritional status of lead-exposed rats, as well as some of the parameters used to assay locomotor activity. When Reiter and Ash (1976a) exposed male rat pups to high doses of lead via their mother's milk (nursing mothers received 5% lead carbonate in the diet), and after 16 days directly through the drinking water (50 ppm), they observed that food consumption was reduced in the lead treated dams with a corresponding reduction in the growth of the pups. Delays in the development of the startle response, eye opening, and righting reflex were observed in both lead-treated and pair-fed animals; thus indicating that these developmental delays may be due to malnutrition. Lead treated animals showed an initial hyperactivity at two weeks, which returned to control levels by six weeks. When locomotor activity in a residential maze was measured in adults, no treatment differences were observed.

When Reiter, et al. (1975) exposed rats, (40 days prior to and throughout gestation and lactation to adulthood) to low levels of lead acetate in the drinking water (5 or 50 ppm), delays in the development of the righting reflex and in eye opening were observed, but body weights were not affected. Locomotor activity of adults males was monitored day and night for five consecutive days in a residential maze. On the first test day hypoactivity was observed in adult lead treated animals during all periods of the activity cycle. On subsequent days, only nocturnal activity was depressed.

Other studies (Grant, et al., 1975; Hastings, et al., 1975; and Sobotka, et al., 1975) using lead exposures not resulting in reduced body weights have not found any persistent changes in the activity levels of the exposed rats.

Thus, all possible variations in locomotor activity (hypoactivity, hyperactivity, no change in activity) as a result of lead treatment have been observed. Some of the confusion is probably due to the wide differences in the doses of lead administered and the concomitant nutritional state of the animals. In most cases no attempts have been made to assess the total body burden of lead, which may vary considerably with the routes of administration utilized. The recent observation by Reiter (1976b), that lead treatment may disrupt the normal activity cycles of rats, may explain some of the conflicting results, since most studies have monitored activity levels for only brief periods of time (hours), rather than for consecutive days. Further research may indicate that depending upon which time period of the daily cycle is monitored, one might observe hypoactivity, hyperactivity, or no changes in activity.

Unfortunately, at the present time, the animal data remain inconclusive.

TABLE 4.1

BEHAVIORAL EFFECTS OF "LOW-LEVEL" LEAD EXPOSURE IN ANIMALS

Reference	Species	Parameters of Lead Administration	Parameters Measured	Effects Observed
Xintaras et al (1967)	Rat (Albino)	1.5 mg lead acetate/kg drinking H ₂ O for several days at 6-7 wks	EEG	Disturbance in REM sleep
Brown, D. R. (1973)	Rat (Sprague-Dawley)	Nursing mothers gavaged (17-35 mg lead acetate/kg) for 20 days after parturition	T-maze learning	Decreased learning
Brown, D. R. (1975)	Rat (Sprague-Dawley)	Lead acetate, either by gavage to the dam or I.P. to the pup	T-maze (visual discrimination) Spontaneous motor activity	Impaired learning no changes in activity
Goode et al (1973)	Rhesus Monkeys	Fed .05 mg-5.0 mg lead acetate in coconut milk for 30 months	Conditioned and delayed response learning	No effect
Allen et al (1974)	Rhesus Monkeys	Infants 0.5 mg/kg lead acetate in formula for 4 wks Adults 20 mg/kg in drinking H ₂ O for 4 wks	"Systematic" observation of behavior	Infants: Hyperactivity, insomnia, abnormal social behavior Adults: No effect
Carson et al (1974)	Sheep	4.2 mg lead/kg body weight in diet four wks before and throughout gestation and lactation	Visual discrimination learning	Performance Deficit
Sobotka et al. (1975)	Rat	Orally; 5, 15, and 44 mg of lead acetate/kg body weight for 3 wks. after birth	General locomotor activity Exploratory activity Passive avoidance Learning behavior	No effects
			Habit-reversal Operant task	Impaired Performance

Silbergeld and Goldberg (1974)	Mouse (CD-1)	Nursing mothers receiving 2-10 mg lead acetate/ml drinking water; at weaning directly through water	Locomotor activity	3-fold increase in activity
Sauerhoff and Michaelson (1973)	Rat (Sprague-Dawley)	27,300 ppm lead acetate to nursing mothers; 25 ppm Pb in diet for 3 wks.	Response to amphetamine, phenobarbital	Amphetamine suppressed hyperactivity; phenobarbital exacerbated it.
Reiter et al (1975)	Rat (Sprague-Dawley)	5 or 50 ppm lead in drinking H ₂ O 40 days prior and throughout gestation and lactation to adulthood	Locomotor activity	40-93% increase in activity
Reiter and Ash (1976)	Rat	Nursing mothers receiving 5% lead carbonate in diet, at 16 days 50 ppm through drinking water	Reflex development Locomotor activity in residential maze	30% reduction in activity
Grant et al (1975)	Rat (Long-Evans)	Stomach intubation .01 - 200 µg lead acetate/g body weight from 1-30 days	Locomotor activity in residential maze	Hypoactivity
Hastings et al (1975)		Nursing mothers receiving 0.2 - 1.0 mg lead acetate/ml drinking water for 21 days	Aggression towards mice	No persistent effects
Brady et al (1975)	Rat (CFE)	Daily oral intubation (500 mg of lead acetate) to both males and females 60 days prior to mating; females throughout gestation and lactation.	T-maze learning operant conditioning	No changes in activity reduced aggression
			Locomotor activity	
			Spontaneous activity	
			Shock-induced aggressive behavior	
			Acquisition and performance of a visual discrimination task (water T-maze)	Performance deficit

CHAPTER 4

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2.0 Effects of Lead on Reproduction

It has been reported since antiquity that lead compounds can be used as abortifacients and that women occupationally exposed to lead have a high miscarriage rate. A recent study by Fahim, et al. (1976) suggests that subtoxic lead absorption during pregnancy may be associated with an increased incidence of preterm delivery and early membrane rupture. A high correlation was found between lead concentration in maternal and fetal blood; both were significantly higher in the preterm pregnancies and early membrane ruptures than in term pregnancies.

Epidemiologic studies (Oliver, 1914) have demonstrated a reduction in the number of offspring in families of workers occupationally exposed to lead. Animal experiments have also shown a reduction in the number of offspring of rats and mice (Schroeder and Mitchener, 1971), and reduced birthweight and survival of animals fed a lead-containing diet (Stowe and Goyer, 1971).

Lancranjan, et al. (1975) have reported that moderate absorption of lead (blood Pb 50-80 $\mu\text{g}/100\text{ ml}$) resulted in diminished fertility of male workers. This appeared to be due to hypospermia and teratospermia. A slightly increased absorption of lead had no effects on the reproductive capacity of exposed workers.

Lead is teratogenic in some species. A urorectocaudal syndrome of malformations was produced in rats exposed to lead during early gestation (McLain and Becker, 1975). Fetal hamsters have shown tail abnormalities when the mother had been given lead (Ferm and Carpenter, 1967). Cardiac abnormalities have been reported after treating chick embryos with lead (Gilani, 1973).

In these studies, high acute doses of lead were administered, usually by intravenous injections. Little is known about the teratogenicity and developmental toxicity of lead following chronic exposure. Kimmel, et al. (1976) exposed female rats chronically to lead acetate via the drinking water (0.5, 5, 50, 250 ppm) from weaning through mating, gestation, and lactation. No teratogenic effects were observed, although exposure to 250 ppm lead acetate caused a slight, but nonsignificant increase in fetal resorptions. The lead-treated animals produced litters of normal numbers, but the offspring from the 50 and 250 ppm groups weighed less at weaning and showed delays in physical development. Reiter, et al. (1975) have also observed developmental delays in offspring exposed to 50 ppm lead throughout gestation and lactation. Whether these delays in development were the result of a direct effect of lead on the nervous system of the pup, or reflect secondary changes (malnutrition, hormonal imbalance, etc.) is not clear. Whatever the mechanisms involved, these studies do suggest that low-level chronic exposure to lead may induce postnatal developmental delays.

There are no convincing reports that lead is teratogenic in humans. An analysis of human fetal tissues (Barltrop, 1969) demonstrated that placental transfer of lead began as early as the 12th week of gestation and that total lead content increases throughout pregnancy, with the highest concentrations occurring in bone, kidney, and liver; but significant amounts were also present in blood, brain, and heart. The quantities of lead present in newborn infants generally reflect that of their mother (Scanlon, 1971); Harris and Holley, 1972; Gershanik, 1974). However, as Barltrop (1969) pointed out, the distribution of lead within the fetus at different stages of development is probably more important than the total amount present at birth.

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Animal studies indicate that significant amounts of lead may be concentrated in the milk of nursing mothers (Green and Gruener, 1974).

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3.0 Effects of Lead on Chromosomes

Contradictory results have been published in the last few years with respect to an increased occurrence of chromosome aberrations in workers occupationally exposed to lead. Bauchinger and Schmid (1970) and Schmid, et al. (1972) found no evidence of increased chromosome aberrations in lead manufacturing workers; or in policemen with increased blood lead levels (Bauchinger, et al. 1972), or in male workers exposed to lead oxide fumes in a shipbreaking yard (O'Riordan and Evans, 1974).

However, an increase in chromosome aberrations in people occupationally exposed to lead has been reported by Forni and Secchi (1972); Schwanitz, et al. (1970), and DeKnudt, et al. (1973). Unfortunately, most of these studies have evaluated very few (10-20) subjects. A study by Forni and Secchi (1972) showed that the rates of chromatid changes were higher in 65 workers with preclinical and clinical signs of lead poisoning but were not significantly raised for workers with past poisoning. Forni, et al. (1976), also examined 11 subjects before and during initial exposure to lead. The increase in rate of abnormal chromatid metaphases was doubled after one month of exposure, was further increased after two months, remained in this stage up to seven months, and then decreased. The fact that most alterations were of the chromatid type (i.e. occurring in cell culture after DNA synthesis) indicates that these may be culture-produced aberrations, not repaired in the presence of lead, and may not reflect a real in vivo situation. Thus its biological significance is unknown.

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3.1 Carcinogenicity of Lead Compounds

Lead has been studied for carcinogenicity and was found to be positive in mice and rats. Earlier experiments were frequently negative but many of them were inadequate.

Positive results were obtained with lead acetate and subacetate in rat and mouse feeding studies. A diet containing 0.1% basic lead acetate fed to Swiss mice produced benign and malignant renal tumors (1). The same compound fed to rats at the 0.1 or 1% level in the diet also produced this type of tumors (2). Renal tumors were also observed in rats fed diets containing 1% lead acetate (3). Benign and malignant kidney tumors were observed in rats fed lead acetate (3 mg/day for 2 months and 4 mg/day for 16 months). Besides the kidney tumors, neoplasms of the testes, adrenals, thyroid, pituitary, and prostate were observed in these Wistar rats (4).

In male Sprague-Dawley rats on a diet containing 1% lead subacetate, two gliomas were observed besides 13 kidney tumors in 17 animals (5).

Subcutaneous injection of lead phosphate, repeated over a 16-months period, produced adenomas, papillomas, and cystadenomas of the renal cortex in albino rats. The total dose of lead administered varied between 120 and 680 mg Pb in the animals getting tumors (6).

No positive findings have been reported on humans exposed to high levels of lead, only negative data were reported by Dingwall-Fordyce and Lane (7) who followed 425 persons who had been exposed to lead in a battery factory. They showed no increases in cancer incidence but an increase in cerebrovascular accidents. This is offered as a basis for the suggestion that species differences in the case of lead toxicity are distinctly apparent. There are

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sufficient publications on ill effects of lead exposure of humans that cases of cancer in these people, even if anecdotal, would have been reported in the literature over the years. Lead is thus not considered a human carcinogen. When the experimental data on rodents are used for extrapolation to human exposure, the equivalent dose for renal tumor development in man would be 550 mg lead per day which appears to exceed the maximum tolerated dose of lead for man (8).

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4.0 Effects of Lead on the Immune System:

In a number of animal species, lead has been reported to increase susceptibility to infection. Hemphill, et al. (1971) found that mice injected with subclinical doses of lead nitrate for 30 days showed a reduced resistance to Salmonella Typhimurium. Selye, et al. (1966) found that rats injected with lead acetate (minimal effective dose 1 mg/100 g body weight) were susceptible to a variety of bacterial endotoxins to which this species is usually resistant.

A number of factors may be involved in producing this decreased resistance to infection. Lead can bind to antibodies (Williams, et al., 1954) and diminishes the level of circulating antibodies (Koller and Kovacic, 1974). Bingham, et al. (1968) found that the inhalation by rats of lead sesquioxide aerosol ($10 \mu\text{g}/\text{m}^3$ to $150 \mu\text{g}/\text{m}^3$) significantly reduced the number of alveolar macrophages. Bruch, et al. (1972) found that rats inhaling particulate lead oxide ($200 \mu\text{g}/\text{m}^3$) showed mitochondrial and endoplasmic reticular damage of alveolar macrophages and pneumocytes, and exhibited a considerable loss in the activity of the benzopyrene hydroxylating enzyme. These studies need further substantiation.

There do not appear to be any systematic epidemiological investigations on the effects of elevated lead levels on the incidence of infectious diseases in man (Hicks, 1972).

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5.0 Experimental Tolerance to Lead

The effects of some metals on the toxicity of simultaneously administered metals, and the occurrence of "metal shifts" in the body have been reported. For example, the prior or simultaneous administration of cobalt (Gabbiani, et al., 1972) or zinc (Webb, 1972) has prevented gonadal atrophy induced by cadmium. Selenium compounds have been found to be protective against the various manifestations of cadmium and mercury toxicity (see Diplock, 1976).

Yoshikawa (1968, 1970, 1974) has reported that prior injections of small amounts of some nonessential metals induced tolerance of a lethal dosage of the same metals given 24-48 hrs. later. The metals which could develop tolerance against their own toxic action were silver, arsenic, cadmium, mercury, indium, and lead. Mice pretreated with some of the essential metals (copper, zinc, iron) did not develop such tolerance. It was also reported that those metals which developed the tolerance could promote cross-tolerance, whereas those which did not induce the tolerance did not promote cross-tolerance. These results indicate that whatever the mechanisms involved, they may be nonspecific, even though metals vary greatly in their physiochemical properties. It has been shown (Suzuki and Yoshikawa, 1974) that the protective effect of pretreatment with small doses of cadmium is probably due in part to the induction of metallothionein. But this mechanism cannot explain the protective effects of pretreatment with lead, which does not induce metallothionein.

Sanai, et al. (1972) and Yoshikawa and Kaneda (1973) have observed that pretreatment with lead results in an increase of fecal lead excretion and a decrease in urinary lead excretion compared to nonpretreated rats. In precreated animals the concentration of blood lead reached a maximum in two

hours, decreased abruptly, and remained stable; whereas in nonpretreated animals, blood lead levels reached a maximum in six hours and then decreased gradually. The ratio of lead levels in red blood cells versus serum was constant in pretreated animals, but increased gradually in nonpretreated animals. Thus pretreatment with small doses of lead causes changes in the distribution and excretion of lead following a subsequent injection of the metal. Similar changes in distribution have been reported for cadmium (Suzuki and Yoshikawa, 1971).

It must be stressed that in all these studies acute doses of the metals are administered via intraperitoneal injections. Whether these interrelationships exist via other routes of administration and at low-level chronic exposures must be elucidated in order for them to be meaningful in the context of environmental pollution.

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5. EMISSION CONTROL DEVICES AND FUEL LEAD ADDITIVES REPLACEMENTS: CHARACTERISTICS AND FATE OF EXHAUST EMISSIONS

1.0 Exhaust Emissions from the Catalytic Muffler

The introduction of the catalytic muffler for automobiles to meet the exhaust emission standards of the Clean Air Act of 1970 for carbon monoxide and hydrocarbons (CFR, Title 40: Part 85.074.1, 1975) has resulted in the use of fuels with lower lead additive contents and fuels with different compositions and fuel additive packages. It was recognized that the exhaust emissions from leaded gasoline could deposit on the active metal surfaces of the catalytic muffler and greatly reduce the oxidizing ability or capacity of the muffler (Bomback, et al. - 1975, Shelef, et al. - 1973). Therefore, in this section of the report, the characteristics and fate of exhaust emissions from the catalytic muffler will be examined in as much detail as possible. Again, the characteristics and fate of the emissions are a function of the fuel composition, and the design features, operating conditions, and age of the catalytic muffler.

1.1 Sulfur Exhaust Emissions from Catalytic Mufflers

The public health impact of the release of sulfate emissions from catalytic mufflers has received considerable attention (Finklea, et al. - 1975, French - 1975). The increased use of catalytic mufflers on light-duty vehicles at the projected release rate of 0.05 g sulfate/mile was estimated to have a large health impact on people living near roadways and commuters who suffer from asthma and other acute and chronic respiratory diseases.

One of the first published records of the increase in sulfate emissions from catalyst-equipped vehicles was reported by Campion (1973). Since that time, Beltzer, et al. (1974) and Somers (1975) have reported on the measurement of particulate sulfate emission rates for many different makes and models of automobiles equipped with catalytic mufflers.

Cadle, et al. (1976) recently reported the results of the General Motors sulfate dispersion experiment with a fleet of 384 automobiles. The maximum sulfate concentration measured in this simulated 4-lane highway driving experiment was $12 \mu\text{g}/\text{m}^3$ above the background level of sulfate. This level was measured at a location near the roadway. At a distance of 100 feet from the roadway, the maximum level of sulfate was $5 \mu\text{g}/\text{m}^3$ above background. The emission for sulfates ranged from 0.003 gm/mile to 0.05 gm/mile. During the experimental study, careful measurements of wind speed, wind direction, and relative humidity were made and incorporated into a dispersion model for determining sulfate concentrations as a function of time and place. The average particle size of the particulate emissions was between 0.01 - 0.1 microns. About 70% of the vehicles were equipped with pellet-type converters and the other 30% were equipped with the monolith-type of converter. The analytical method for sulfate did not determine what cation the sulfate anion was associated with. The sulfur content of the fuel ranged from 0.028 - 0.032 weight percent. The other components of the fuel were not specified.

In experiments conducted by the EPA during the GM study, Whitby, et al. (1976) determined aerosol size distributions for sulfate emissions. These emissions were characterized by a trimodal-type of distribution: Mode 1 was nuclei material, 0.005 - 0.05 microns; Mode 2 was fine material, 0.05 - 1.0 microns; and Mode 3 was coarse material, 1 - 30 microns. Tanner and Newman (1976) determined that the sulfate emission was sulfuric acid. The concentration of sulfuric acid mists near the roadway were $3-6 \mu\text{g}/\text{m}^3$. This emitted sulfuric acid reacted rapidly with ambient ammonia to produce $(\text{NH}_4)_2 \text{SO}_4$. The half life of the reaction was about 10-100 seconds, depending on the amount of ammonia available in the atmosphere.

In a different study conducted for the EPA by Exxon Research and Engineering (1975), sulfate emission rates for 20 automobiles of various makes and models were determined as a function of accumulated mileage. For sulfate emissions the average results for the 20-car fleet showed a rapid use from 0.006 g/mile at 0 accumulated miles to 0.021 gm/mile at 4,000 miles. This rise was attributed to the storage phenomena of the catalytic muffler. Then the exhaust emission rate declined to 0.006 gm/mile at 32,000 miles. This decline was attributed to the reduction in oxidizing ability of the catalyst to convert sulfur exhaust emission to SO_3 . The 20-car fleet was purchased in California. The 1975 California exhaust emission standards for CO are 3.4 gm/mile, for hydrocarbons 0.41 gm/mile, and nitrogen oxides, 2.0 gm/mile. It was important to note from the results of this test that the CO emission rate ranged from 4.0 - 5.2 gm/mile for 0-32,000 miles; hydrocarbon emission rates ranged from 0.4 - 0.8 gm/mile; and nitrogen oxides ranged from 1.6 - 1.7 gm/mile. The average lead content of the fuel was 0.03 gm Pb/gal. and the average sulfur content was 300 ppm.

The poisoning effect of the platinum/palladium catalytic surface by the fuel additive package of TEL and the lead scavengers, ethylene dichloride and ethylene dibromide, has been studied by Otto and Montreuil (1976). TEL at a concentration of 0.5 gm/gal, without scavengers caused the most severe loss of oxidizing ability of the catalytic surface. In this study, oxidizing ability or capacity was related to the amount of Pt/Pd surface area available. For the fuel containing 0.5 gm Pb/gal as Motor Mix (both scavengers present) the oxidizing ability of the catalytic muffler was reduced to about 30% of its original ability after 10,000 accumulated miles. After 50,000 miles, the

oxidizing ability had been reduced to 10% of its original value at 0 accumulated miles. These results were compared to unleaded iso-octane fuels which did not reduce the oxidizing ability of the active surface at such a rapid rate. In addition, it was shown that the scavenger, ethylene dibromide, had the most severe, but reversible effect on oxidation of CO and hydrocarbon emissions.

The atmospheric transport of particulate sulfur emissions has been studied by Roberts and Friedlander (1975) for the Los Angeles Basin. From the transport model used to estimate gas to particle conversion rates for sulfur, it was estimated that the introduction of catalyst-equipped vehicles could add significantly to the particulate sulfur concentrations measured at locations downwind of the release points.

1.2 Release Rate of Catalyst Components to the Environment

Along with the sulfate emissions, the release of the components of the catalytic muffler to the environment has been the subject of several experimental studies. The basic components of the muffler are platinum and palladium, about 3 gm/muffler, which are applied to an alumina substrate. The two designs of catalytic mufflers are the monolith or fixed bed reactor, and the pelleted or fluidized bed reactor.

Brubaker, et al. (1975) raised the issues of release and fate of platinum in the environment. In the GM study (Cadle, et al. - 1976), an emission rate for platinum of 20 $\mu\text{g}/\text{mile}$ was determined. There was no information on chemical form of emitted platinum, and no information on particle size. Taylor and Hanna (1975) have reported on the ability of methylcobalamin (MeB-12) to form a moderately stable methylated form of platinum when incubated with μM levels of K_2PtCl_6 .

2.0 Exhaust Emissions from Catalytic Mufflers from the Use of Fuels with Higher Aromatic Content

Gasolines of all grades contain a certain weight percent of aromatic organic chemicals. The chemicals most frequently used are benzene, toluene, and the xylene isomers because they increase the Research Octane Number (RON) and prevent pre-ignition or knock of gasoline. The highest percentages of aromatics are used in premium grades of fuel. The percentage of aromatics in unleaded premium fuel is greater than leaded premium fuels. The major public health concern with the combustion of unleaded fuels containing high weight percents of aromatics is the exhaust emission of particulate matter which has polynuclear aromatic compounds adsorbed to a carbon core (NAS-1972).

Gross (1973) presented data on how exhaust emission of polynuclear aromatic (PNA) compounds were a function of the engine modification emission control system, the amount of polynuclear aromatic content of the fuel and the oil consumption rate. For the 1968 vehicles, the emission control system was an air-injected RAM thermal reactor; the 1970 vehicle control system was a monel + platinum catalytic muffler, Engelhard PTX-5. Emission control systems for 1968 and 1970 model vehicles reduced PNA emissions by 65-85% relative to the uncontrolled vehicle. PNA content in fuel was linearly related to the PNA emission rate. The indicator PNA chosen for identification was benzo(a)pyrene (BaP). High oil consumption caused higher emission rates of PNA's.

The major variables effecting BaP emission rate were summarized by Gross (1973) as follows:

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BaP in Fuel ppm	Oil Consumption	No. Emission Control	BaP Emission $\mu\text{g/gal.}$ Engine Modification	
			1968	1970
0.01	Normal	130	41	26
0.4 - 0.5	Normal	290	68	47
3 - 3.2	Normal	800	200	170
0.4 - 0.5	High due to valve seal removal	-	-	150
0.4 - 0.5	High due to oil ring removal	-	7600	-

A minor factor in the emission rate of PNA's was the synthesis of PNA's from simpler aromatic molecules. Previous data from Gross (1972) had showed that PNA emission rate increased sharply as aromatic content increased from 11% to 46% by weight. Fuel lead and phosphorous content of fuel did not have much influence on emission rates. PNA's tended to accumulate in engine motor oil. The mechanism of PNA emission was similar to emission of lead particulate emission; i.e. a strong function of mode of driving and age of the exhaust system. Other PNA's which have carcinogenic activity and have been identified by Grimmer, et al. (1972) and Boyer and Laitinen (1975) are dibenz(a,h)-anthracene, chrysene, and benzo(a)anthracene.

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3.0 Exhaust Emissions from the Fuel Additive Methyl Cyclopentadienyl Manganese Tricarbonyl: MMT

The manganese fuel additive methyl cyclopentadienyl manganese tricarbonyl (MMT) is currently used in the motor mix fuel additive package. It acts both as a promoter for TEL and as an antiknock compound in its own right. Recently, consideration has been given to using MMT as a replacement for TEL. No scavenger compounds would be required, and the optimal concentration for use in gasoline would be 0.125 gm Mn/gal. (Ethyl Corporation - 1971, 1972, and 1974a). At this use level, the road octane number of gasolines would be increased by approximately 2.2 units. In addition, it was stated that manganese exhaust emissions would not effect the efficient operation of the catalytic muffler. There was no data given to support this claim. At higher use levels (1 - 2 g Mn/gal.), spark plug life was significantly shortened. The major form of manganese in exhaust emissions was Mn_3O_4 . Typically about 0.1% of the MMT was emitted from the tailpipe unburned. In the 1975 lean reactor cars, this level of unburned MMT in the exhaust was reduced to 0.01 - 0.02%.

Ter Haar, et al. (1974) have studied the photolytic decomposition of MMT in the vapor phase. Major decomposition products were manganese oxides and carbonates. $Mn_2(CO)_{10}$ was not detected. The organic portion of the solid materials appeared to be a complex mixture of acids, esters, and hydrocarbon amorphous polymers resulting from the partial oxidation of the cyclopentadienyl ring, CO insertion reactions, and polymerization of multifunctional compounds. It was estimated that the half life of this reaction was 15 seconds.

Using the 7-mode Federal Test Cycle, Ter Haar, et al. (1974) reported that the average FMED for manganese exhaust emissions from the combustion of

fuel containing 0.125 g Mn/gal., were 0.38 μ for cold cycles and 0.30 μ for hot cycles. A comparison with lead emissions from a fuel containing 0.5 g Pb/gal. gave an average MMED of 0.4 μ for cold cycles and 0.32 μ for hot cycles. There was no information given on emission rates of manganese particulate emissions. It was stated that 2/3 of the particles were of a size that they would remain suspended for some time.

There has been considerable concern about the role of particulate manganese in the catalytic oxidation of SO_2 to SO_3 . Gerhard and Johnstone (1955) found that the photochemical oxidation rate of SO_2 to SO_3 was 0.1 - 0.2% per hour, with the rate being dependent on the relative humidity. Assuming first order kinetics, this gave a rate constant of about 0.002 (hours)⁻¹. McKay (1971) studied the atmospheric oxidation of SO_2 in the presence of NH_3 . At NH_3 levels of 10 $\mu\text{g}/\text{m}^3$, McKay predicted that the conversion of SO_2 to sulfate would be greater than 50% per hour. Again assuming first order kinetics, the rate constant was 0.69 (hours)⁻¹. Ambient levels of NH_3 have been reported by the PHS (1966) are above 20 $\mu\text{g}/\text{m}^3$. In simulated atmospheres containing NH_3 , SO_2 , and Manganese particulate emissions, Wright, et al. (1974) have studied the effect of manganese exhaust emissions on the oxidation of SO_2 in air. It was estimated that if all gasoline contained 0.1 gm Mn/gal., this would increase ambient manganese concentrations in urban air by 0.02 to 0.2 $\mu\text{g}/\text{m}^3$. Average yearly ambient concentrations of 0.02 - 0.05 $\mu\text{g}/\text{m}^3$ (NAS-1973). Wright, et al. (1974) demonstrated that in their simulated atmosphere contained in a black bag, that manganese concentrations did not have a significant effect on the rate constant for oxidation of SO_2 until levels greater than 20 $\mu\text{g}/\text{m}^3$ were reached. Below this concentration, the rate constant was constant at 0.14 (hours)⁻¹.

Ethyl Corporation (1974b) has stated that the presence of manganese exhaust emissions resulting from the combustion of gasoline containing 0.125 gm Mn/gal. does not pose a public health problem. From the lack of information on emission rates, size of particles, deposition rates and partitioning in the environment, the bases for this statement is questionable. In addition, there is very limited information on chronic exposure to low levels of manganese oxide (Stara - 1973). High levels of industrial exposure to MnO_2 particles in air (50 - 60 mg/m^3) have produced a neurological disorder similar to Parkinsonism and a respiratory disease similar to acute lobar pneumonia (Mena, et al. - 1967, Canavan, et al. - 1934, Van Beukering - 1966, Mena, et al. - 1969, Emara, et al. - 1971, Davies - 1946, Rodier - 1955, Morichau-Beauchant - 1964, Gabuniya - 1964, Tanaka and Lieben - 1969, and Louria, et al. - 1972). In addition there is no information on chronic exposure to low levels of manganese oxides both in ambient air and dust and dirt for young children, pregnant women, and susceptible segments of the population.

The parent compound, MMT, has an LD_{50} value of 56 mg/kg by oral administration to mice (Strohmeier - 1964). The TLV (ACGIH - 1974) for MMT has been given as 0.1 ppm. Additional information on the geochemistry, uptake by plants, and discussion of manganese as an essential trace element are reviewed by the NAS (1973).

4.0 Alternative Fuels

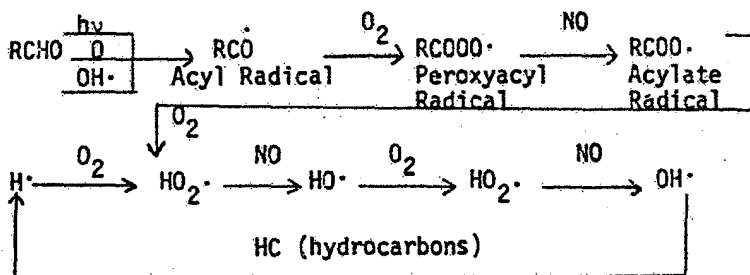
The use of alternative fuels for gasoline has been suggested and practiced to some degree since the early 1930's. In Europe, particularly, the use of ethanol and methanol blended with gasoline has been a common practice. It has only been recently, however, as a result of uncertain supplies of crude oil that serious consideration has been given to alternative fuel use on a massive scale in the United States.

The NAS (1973b) has reviewed the status of proposed alternative fuels. The three candidate fuels are liquified natural gas (LNG), hydrogen, and alcohols. Natural gas, composed mainly of methane and propane, is expensive, does not improve drivability, and does not offer any great advantage over current grades of gasoline in reducing the quantities and types of air pollutants. Hydrogen, however, offers many advantages in terms of air pollution reduction since there is no carbon present. Therefore, exhaust emissions of CO and unburned hydrocarbons do not exist. Its high flammability range means that very lean mixtures can be used so that nitrogen oxide emission rates are reduced because of the lower combustion chamber temperatures. Another advantage is the absence of sulfur, thereby eliminating exhaust emissions of SO₂. However, neither the industrial capacity nor the automotive engine-fuel delivery system are available on a large scale.

Alcohols, particularly methanol, alone or blended with gasoline have been used for fuels in spark-ignited engines for some time. Reed and Lerner (1973) reviewed the benefits of methanol as a fuel in many applications. As an alternative fuel for gasoline, methanol has a lower heating value and requires the addition of volatile chemicals to aid in starting during cold weather. The main advantage of methanol as a fuel was given by the NAS Report (1973b)

as the reduction of nitrogen oxide emission rates. These lower emission rates were the result of leaner mixtures which produced lower combustion chamber temperatures. This reduction in nitrogen oxide emission rates was supported by the research reports of Adelman, et al. (1972), Ebersole and Manning (1972), Tillman, et al. (1975), Most and Longwell (1975), and Ingamells and Lindquist (1975). Bolt (1964) and the API (1971) contended that the use of alcohols as fuels in automobiles did not appreciably reduce air pollution. This view was supported by Brinkman, et al. (1975), who demonstrated reductions for CO emissions, but no significant changes in hydrocarbon or nitrogen oxide emission rates for a 10% methanol - 90% gasoline blend. In addition, drivability and fuel economy were reduced.

The API (1971) report states that use of alcohols results in increased emissions of aldehydes. Aldehydes are very reactive chemicals which can significantly contribute to the atmospheric chemical reactions which convert NO to NO₂ without consuming ozone. This reaction sequence is given by Seinfeld (1975) as:



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Posner (1975) recently reviewed the biohazards of methanol in its proposed new uses. The human biohazards were discussed in eight categories: hazards at young ages; potential interactions; abuse; delayed and irreversible toxicity; dermal and inhalation hazards; toxicity of formaldehyde combustion products; nearly invisible flame; and a larger storage volume required for an equivalent energy return as compared to gasoline. Several suggestions were given to reduce the hazards associated with methanol use, but it was concluded that methanol produced known delayed and irreversible effects and was a difficult chemical to control.

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