# Meetings

## Prague International Lead Panel: Effects of Atmospheric Lead on Biological Systems

Relevant to the present debate on the effect of atmospheric lead on biological systems are the discussions of an international panel at the Charles University in Prague, Czechoslovakia, 15 October 1970. These discussions highlighted worldwide concern for potential damage to human health from minute concentrations of lead in the atmosphere. The panel presented information on sources of lead, kinetics of lead absorption, distribution and excretion, sensitive biologic measures of the body burden of lead, and biochemical and clinical features of lead poisoning.

Lead in air was measured in several large cities in Japan. The average value for all samples was 0.51 $\mu g/m^3$ with a maximum value of 2.04 $\mu g/m^3$ (24-hour samples). These values were lower than those obtained in Los Angeles, Cincinnati, Philadelphia, and other U.S. cities by the Environmental Protection Agency. There was a suggestion that the lead concentration in the atmosphere of Osaka Prefecture had increased during recent years (Horiuchi). Interestingly, normal healthy Japanese adults in Osaka City showed amounts of lead in urine in 1969–70 (37.0 $\mu g$/liter) similar to those seen in 1950–55 (35.5 $\mu g$/day). However, the lead concentration in whole blood was greater in 1969–70 (29.6 $\mu g$/100 g) than in 1950–55 (11.0 $\mu g$/100 g). This increase, which may be due to increased automotive traffic and greater utilization of leaded gasoline, elicited cause for concern.

Lead smelters in the Slovenian Alps were reported to be polluting the atmosphere and contaminating the soil, plant life, and rivers of adjacent valleys (Djurić). Only part of the lead in the soil was available for uptake by plants. Vegetables showed selective absorption of lead into the edible portions. For example, parsley, rutabaga, and beets absorbed large quantities of lead; but onions, garlic, and potatoes absorbed much less.

The distribution and excretion of lead in animals were described by a power function model consisting of several compartments (Piotrowski). The blood and internal organs comprised a "rapid exchange pool." Muscle and skin represented an "intermediate pool." (However, in one study on rats it had been reported that there was no significant accumulation of lead in muscle and skin, but in a study on rabbits it had been reported that muscle played an essential role as a reservoir of lead.) The skeleton, the major storage site for lead, constituted a "slow exchange pool." However, the skeletal lead may actually be better described in terms of several compartments, including an "irreversible deposit." Experiments with rabbits indicated that lead deposited in cortical bone is firmly bound and may be only slowly eliminated over many years; but lead stored in trabecular bone is not very firmly bound and is excreted readily after exposure so that about 80 percent of the lead excreted in urine is of skeletal origin. It was emphasized that animal models for kinetics of lead metabolism do not appear to fit many of the observations in man. Further studies in humans are necessary with particular attention to changes occurring over short exposure time periods.

According to long-term studies of humans conducted in the United States and in Japan, the absorption of lead via the digestive tract ranges from 5 to 15 percent, depending on concentration (Horiuchi and Pfitzer). These values represent effective absorption as determined by balance of lead between oral ingestion and fecal elimination. The contribution to total excretion of lead assimilated through the airways was not determined. Although lead can be found in the bile, the extent of enterohepatic circulation of lead is not known. Experiments wtih rats have shown as little as 1 percent of lead absorbed via the digestive tract.

Inhalation of lead may be a major factor in some industrial environments and may be significant in urban areas also (Pfitzer and Teisinger). There are as yet no definitive studies in man to establish the magnitude of absorption of lead particles from the lungs. The importance of size of lead particles in air was noted especially with regard to deposition and retention of such particles in the airways of lungs. The aerodynamic diameter of lead aerosols in most environments averages about 0.15 to 0.3 $\mu m$. Depending on pulmonary ventilation rates, approximately 40 to 60 percent of these particles are not deposited and leave the lungs with the exhaled air. The remaining particles are deposited primarily in the pulmonary spaces where they are subject to (i) clearance to the gastrointestinal tract via the mucociliary escalator, (ii) removal to lymph nodes, or (iii) solubilization and absorption into the blood. According to long-term studies of humans in the United States, 100 percent of the deposited lead particles of this size range are absorbed into the blood (or about 50 percent of inhaled particles) as indicated by the indirect evidence of failure to demonstrate significant clearance of lead from the lungs to the feces. A report from Japan estimated the absorption of the deposited particles at 50 percent (or 25 percent of inhaled lead particles). A theoretical model for deposition and clearance proposed by the International Commission for Radiation Protection predicts the absorption of about 10 percent of inhaled particles of this small size. There are as yet no definitive studies in humans to establish a more precise value for the range of 10 to 50 percent absorption of inhaled lead particles as given above. It is expected that solubility characteristics of different lead compounds in body fluids will affect absorption. It has been shown in man that larger lead particles (2 $\mu m$ in actual diameter) were deposited primarily in the upper airways and led to an increased elimination of lead in the feces.

The overall absorption of lead into the body with the relative contributions due to ingestion and inhalation was discussed (de Bruin). The information needed includes the daily consumption of food and beverages, the concentration of lead in food and beverages, the effective absorption factor from the digestive tract, the volume of air breathed per day, the concentration of lead in air, the fraction of lead deposited in

the lungs, and the fraction of lead absorbed into the blood from the lung surface. As noted above, some of these values are not known precisely. Concentrations of lead in air, food, and beverages may vary from country to country or from urban to rural areas. In addition some of the panel members used different normal values for respiration or for dietary consumption. A model for calculating the overall absorption was presented for which more precise data may be incorporated as they become available.

There were some semantic difficulties about the concept of "biologically active" lead. For example, biological activity may imply actual reactions of lead with components of the body resulting in measurable changes in function, structure, or concentration of normal body chemicals, or it may imply the simple mobility of lead through the body with only the potential for the above reactions.

The well-known effect of lead on heme synthesis was reviewed (Hernberg) briefly with major emphasis placed on findings with δ-aminolevulinic acid dehydrase (ALAD). A significant negative correlation exists between the concentration of lead in blood and the activity of this enzyme in circulating erythrocytes. This correlation exists within the normal range of lead concentration in whole blood (10 to 50 μg/100 g), as well as at high concentrations. In Finland, new employees in the lead industry were studied weekly from the time of their preemployment clinical examinations through the initial months of their work exposure. The gradual increase of lead in blood and the gradual decrease of ALAD activity in blood were essentially mirror images of each other. Workers in Czechoslovakia who 3 to 17 years ago had been treated for chronic lead poisoning were reexamined. In most patients where the calcium ethylenediaminetetraacetate (CaEDTA) mobilization test indicated that a significant body burden of lead existed, there was a decrease in ALAD activity. However, there was no indication that this change in enzyme level had any influence on the health of these patients. The significance of decreased ALAD activity in peripheral blood remains unknown insofar as the health of man is concerned, even though the ALAD activity appears to be a sensitive indicator of absorption of lead from the environment.

Other relatively sensitive biologic measures of absorption of lead were presented (Xintaras), including (i) the influence of lead on pulmonary macrophages with the implication of this effect on lung defense mechanisms against bacterial and viral infections; and (ii) the effects of lead on brain and behavior with the use of objective measures of nervous system activity, such as electroencephalography, rapid eye movement (REM) sleep patterns, nerve conduction, and classical conditioning or operant behavior techniques. It was suggested that neurochemical assays and alterations of drug metabolism may be promising areas for further research on dose-response and studies on mechanisms.

Lead workers in Germany were examined for chromosomal changes (Lehnert) in the leukocytes of the peripheral blood. In workers with blood lead from 62 to 89 μg/100 ml, a general positive correlation between an increase in urinary δ-aminolevulinic acid (ALA) and the percentage of abnormal mitoses was reported. The predominant chromosomal aberrations occurring in the leukocyte cultures were of the gap and break type, and most of these findings were statistically significant relative to a control population. Lead acetate solutions ($10^{-4}$ to $10^{-6}M$) added to normal leukocyte cultures produced the same chromosomal anomalies as noted above. The relationship of these chromosomal aberrations to similar changes produced by caffeine and other common drugs is not yet known.

It was stated that many atypical clinical features of reported lead poisoning are simply coexisting disturbances that are not in fact caused by the lead exposure (Beritić). Clinical results were presented on 300 cases of severe lead poisoning in Yugoslavia from 1945 to 1970. No evidence of hypertension or premature atherosclerosis as the sequelae of lead poisoning was noted. The most reliable, simple clinical test for lead poisoning was excessive basophilic stippling of erythrocytes. In 64 cases with lead colic, 13 had blood lead concentrations less than 80 μg/100 ml. Other panel members also reported cases with clinical symptoms of lead poisoning at blood lead concentrations below 70 μg/100 ml.

Blood lead concentrations, as evidence for or against lead poisoning, must be interpreted with special consideration for their time pattern relative to onset and persistence of symptoms. It was reported by panel members that symptoms of lead intoxication may be persistent and that, particularly in acute episodes, the blood lead concentration may change markedly after the initial onset of symptoms.

Experience with cases of lead poisoning in Sweden and Finland led to a proposed classification system of five groups. An attempt was made to provide a semiquantitative measure (Cramer) of severity of lead intoxication by a scoring system for various symptoms and clinical tests. There was considerable disagreement among panel members regarding objective measures of specific symptoms and the relative weighting of one symptom compared to another.

The consensus of the Prague International Lead Panel was that the present levels of lead contamination for the general population have no measurable adverse effects on health. However panel members indicated that more sensitive tests were needed for the recognition of subtle responses to environmental lead exposure in the most sensitive groups in the general population.

The discussion was part of a conference on chemical pollution and human ecology held 12 to 17 October 1970 under sponsorship of the International Association of Occupational Health. The panel members were J. Teisinger, chairman (Institute of Industrial Hygiene and Occupational Diseases, Prague, Czechoslovakia); K. Horiuchi (Osaka City University Medical School, Japan); D. Djurić (Institute of Occupational and Radiological Health, Belgrade, Yugoslavia); S. Hernberg (Institute of Occupational Health, Helsinki, Finland); J. Piotrowski (Institute of Occupational Medicine, Lodź, Poland); C. Xintaras (Environmental Protection Agency, Cincinnati, Ohio); G. Lehnert (University of Erlangen, Nürnberg, Germany); E. Pfitzer (University of Cincinnati, Cincinnati, Ohio); A. de Bruin (University of Amsterdam, the Netherlands); T. Beritić (Institute of Medical Research and Occupational Health, Zagreb, Yugoslavia); and K. Cramér (University of Göteborg, Sweden).

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