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Statement of Robert A. Kehoe, M.D.
at a Public Hearing of the Division of Air Pollution Control
of the Department of Health of the Commonwealth of Pennsylvania
in relation to
Ambient Air Quality Criteria
with respect to
Particulate Compounds of Lead (Dated Feb. 1, 1967)

I, Robert A. Kehoe, represent the Kettering Laboratory, in the Department of Environmental Health, of the College of Medicine of the University of Cincinnati, Cincinnati, Ohio. Since my retirement, at slightly beyond the conventional age, from the Directorship of this Laboratory and Department, in 1965, I have continued to be responsible for the Laboratory's experimental program on the behavior of lead in the human organism. This program, carried out for many years with the financial support of industry, is now so sponsored by a group of industrial organizations and by the United States Public Health Service.

For the past five years, this work has been concentrated on the establishment of criteria for arriving at a standard of quality, with respect to the concentration of lead in the ambient atmosphere that is tolerable for human beings, when taken into the respiratory system, along with that which is taken into the alimentary tract from other sources in the general environment, in particular, that contained in our food and beverages. I am here to describe the progress and the present position of these investigations.

Another reason for my appearance arose from the fact that certain information which I provided in public testimony before the Muskie Committee in Washington, D.C., some months ago, has been made the basis for a calculation, by this agency of the Commonwealth of Pennsylvania, of the maximum concentration of lead in the ambient atmosphere, which may be expected to be compatible with public safety. The figures given at that time were not provided for that purpose, and the concentration of atmospheric lead which was obtained through their use is too low,

in my opinion, to be realistic, for the reason that a factor of considerable magnitude was not taken into account in this calculation. I shall return to this point later.

To resume the discussion of the experimental work which has provided the background for the present statement and those made elsewhere, my associates and I, in the Kettering Laboratory, have been engaged for the past twenty-eight years, in a descriptive elucidation of the metabolism of lead in human subjects under a variety of conditions. These investigations have established the general level of the intake of lead in the food and beverages consumed by healthy male subjects, and in the output of lead in their urine and feces, day by day over periods of months and years, under the ordinary conditions of life, excepting as the subjects have guarded against any occupational or other unusual exposure to lead. To certain of these subjects, lead in a series of dosages has been administered daily, with their meals, with the objective of determining the extent of the absorption and the excretion of lead, under these conditions, and the amount of lead that accumulated in their bodies during periods of experimental administration that ranged from 1 to 4.5 years. As a by-product of these observations, the maximum quantity of lead ingested daily in food and beverages, which would result in a barely demonstrable increase in the rate of the excretion of lead in the urine, without any corresponding increase in the concentration of lead in the blood, was determined. This quantity, approximately 0.6 mg. of lead, ingested daily, resulted in the accumulation in the tissues of the subjects of an amount of lead of the order of 8 milligrams per year. From these facts, it may be taken that approximately 0.5 milligram of lead, on the average, can be ingested daily by the healthy American adult, without any risk, so long as the concentration of lead in the ambient atmosphere does not exceed, appreciably, the level that it was known to be in the pertinent area of Cincinnati during that period (approximately 1.5 micrograms per cubic meter).

The experiments concerned with the inhalation of lead in the atmosphere, under the conditions of the laboratory, in which we have been engaged, for the past 16 years, have not been quite so revealing of precise information, for two reasons. The more potent of the two reasons lies in the fact that there has been no satisfactory method for measuring the extent of the absorption of lead from the respiratory tract. The other reason stems from the virtual impossibility, within the limits of reasonable costs, of maintaining human subjects continuously in an artificial atmosphere, with respect to its uniform content of lead. For various reasons, an experimental effort has gone about as far as it is practicable to go, in this direction, when the subjects are required to spend 84 hours per week (half of their time) in respiratory chambers.

Accurate measurement of the ultimate degree of the retention of particulate lead in the respiratory system, following the inhalation of lead in the atmosphere, constitutes the obstacle to a satisfactory estimate of the quantity of lead available for absorption. The approximate quantity of the air-borne lead that is retained in the respiratory system during a definite period of exposure can be determined by a method which we have employed at weekly intervals throughout most of these experiments.(by measurement of the lead content of the expired air and subtracting this amount from the lead content of the air in the chamber). But the ultimate degree of the clearance of the particulate lead deposited within the respiratory tree, and moved subsequently to the alimentary tract, by various mechanisms, is not determinable unless it can be visualized in its proper quantitative relation to that which has been ingested with food and beverages. When one breathes without respiratory protection, in an atmosphere heavily laden with particulate lead compounds of relatively large size (1.5 microns or more in diameter) lead appears in the feces in quantities (milligrams) that stand out sharply against the quantities (averaging 0.2 or 0.3 mg. per day) derived from food and beverages.

However, when the concentration of lead in the air breathed for several hours per day is only a few micrograms per cubic meter, as in our experiments, the quantities of lead cleared into the alimentary tract are too small to exceed the variability of the fecal lead (due to ingested food), and also too small to be identified above the variability and the sampling error of the lead in duplicates of the food consumed from day to day - that is, of course, too small to have statistical significance./ It has been apparent, in our respiratory experiments, that the excretion of lead in the urine of the subjects (which is expected to have a well-defined relationship to the amount of the absorption of lead from the respiratory tract) has not increased, under controlled experimental conditions, to the extent anticipated, had all of the lead retained during the respiratory cycle been available for absorption. Only recently has there been any valid basis for ascribing numbers to the actual clearances of lead from various parts of the respiratory tree. Hithertoo, in stating the facts observed in our experiments, we have made no attempt to express these physiological phenomena in quantitative terms, but, instead, have given them qualitative recognition in the statement that "somewhat less than 50 per cent" of that inhaled is retained in the pulmonary tree and is available for absorption. In one instance, I estimated, roughly, that approximately 20 per cent of that inhaled, appeared to be absorbed.

I shall return, a little later, to consider the outcome of the calculation referred to above, when the factor of the clearance of deposited particulate lead is included, according to the best information now available. Meanwhile, attention should be given to a means of overcoming the obstacle presented by the necessity of resorting to <u>intermittent</u> rather than <u>continuous</u> respiratory exposure in our experimental approach to the problem of lead in the ambient air. A crucial experiment has established a basis that is believed to be sound.

Previous experiments, concerned with the daily ingestion of sufficient quantities

of lead with meals had shown that the rate of the excretion of lead in the urine, and the concentration of lead in the blood increased at a substantially constant yearly rate (with seasonal and other variations within the year) over the entire period of the administration of lead in this manner. In contrast, the experimental inhalation of lead, on a temporal schedule simulating that of the industrial week (37.5 to 40 hours per week) resulted in a fairly steady increase in the output of lead in the urine, and in the concentration of lead in the blood, over a period of approximately 16 weeks, at which time a plateau had been reached (in the levels of lead in urine and blood) which remained unchanged thereafter, until the experimental exposure was altered or terminated. With these facts in mind, an experiment was designed and carried out wherein two persons, in parallel respiratory chambers, were subjected to the inhalation of a suitable compound of lead (the sesquioxide), in fine dispersion (mean diameter 0.05 micron) in the atmosphere of the chamber, at the level of 150 micrograms per cubic meter. The schedule of exposure was initiated at 10.5 hours per week for 16 weeks, and expanded stepwise to 21, 31.5 and 42 hours per week, during three additional periods, each of which was 16 weeks in duration. The result was a series of plateaux of graduated height in the concentration of lead in the blood (and in the urine), so that a line connecting the average levels of the successive plateaux continued upward at a uniform slope, and could be extended at the same slope to 168 hours per week. By such means, a reasonable approximation to the effect of continuous exposure could be arrived at.

Proceeding from this background, a further experiment was carried out, with new experimental subjects, at the level of 10 micrograms per cubic meter in the atmosphere of the chambers. Under these conditions, this concentration of lead in the atmosphere failed to evoke a definitive increase in the output of lead in the urine, or in the concentration of lead in the blood, of the subjects, at any time in the course of a schedule that extended in a graduated series from

10.5 through 73.5 hours per week. The exposure of the subjects was terminated at the latter point, since there was no hope of demonstrating a graduated increase in their response. An additional experiment was then initiated at the level of 20 micrograms of lead per cubic meter under otherwise comparable experimental conditions. This experiment is now under way but has not reached the stage at which any prediction as to the probable outcome can be made.

Any estimate of the tolerable concentration of lead in the ambient air, that might be made at this time, through a calculation of the type referred to above, would have to be highly tentative, in our view, especially since experimental evidence may be expected to be forthcoming within a reasonable period of time. It would seem to be logical, however, as suggested above, in representing the immediate situation to this agency of the Commonwealth of Pennsylvania, to make use of the method of calculation employed in arriving at the figure of 5 micrograms of lead per cubic meter as the upper tolerable limit of the concentration of lead in the ambient air, (reference is made here to the two letters of Victor H. Sussman to Robert A. Kehoe, of December 15 and 20, 1966). In so doing, it is appropriate to introduce the factor which appears, on recent evidence, to have a reasonable degree of quantitative validity.

Attached hereto is a chart, Table 1, derived from a publication that has just come to hand. In it, the reference to the publication is given, as are also the data obtained therefrom that are pertinent to our experimental conditions. These data have been employed, in round numbers, in the calculation of the tolerable concentration of lead in the ambient atmosphere, as follows:

(1) If approximately 10 per cent (in the chart 9.5%) of the lead inhaled from the atmosphere in our experiments is available for absorption from the respiratory tract; (2) and if an additional 10 per cent of that deposited originally in the respiratory tract and then moved into the alimentary tract is absorbed from the alimentary tract; (3) the figure thus obtained now turns out to be 18 micrograms

per cubic meter.

The figure so obtained above is not necessarily or even probably correct. Experimental evidence is required for its verification or correction, as the case may be. It has, however, a rational basis for its derivation, and, as such, it would seem to be the best estimate that can be offered as an approach to a suitable criterion.

One other point requires some consideration here. A factor which enters into the promulgation of a standard of air quality, with respect to lead in the ambient atmosphere, is that of the allowance that should be made for the variability in the susceptibility of persons and groups in the composition of the general population. There is no acceptable convention that has the slightest rational applicability to this physiological problem. A considered opinion may now be based reasonably on the evidence obtained by clinical observations in association with quantitative measurements of environmental conditions in the lead trades and in the community generally, and on the physiological and clinical responses of large numbers of persons to such environmental conditions. Such observations, made only in the comparatively recent period within which analytical facilities have been equal to the task (approximately 30 years), have demonstrated, beyond any reasonable doubt, that human susceptibility to the effects of the absorption of lead varies only within well-defined quantitative limits of absorption. When, for example, the industrial environment (in the lead-using industries) is maintained faithfully below certain established hazardous levels, and when all of the conditions under which the employees work are so controlled that their absorption of lead does not exceed the accepted level of safety, no toxic effects of any kind are observed at any time in any person during the most prolonged periods of employment that American industry affords. Similarly, the occurrence of lead poisoning within the general population, among children and adults alike, is always associated with levels of lead absorption (as shown by the lead content of urine or blood or

Conversely, in our experience, no person suffering from lead poisoning has been found, at the onset of this illness - that is, in immediate temporal relationship to the exciting factors in the production of such illness - who has not given quantitative analytical evidence of the absorption of dangerous quantities of lead. (By such evidence, here, is meant a general level of excretion of lead in the urine, established through adequate sampling, of at least 0.15 mg. per day or per liter, or a concentration of at least 0.08 ± 0.01 mg. per 100 grams of whole blood, as determined by methods of analysis as sensitive and precise as those employed in the Kettering Laboratory.) Such evidence as this, obtained by a number of experienced investigators during the past thirty years, has demonstrated that human susceptibility to lead poisoning, manifests itself, often, at and above a certain level of absorption, but not below it, and that the margin between the dangerous level of absorption and that which is associated with ordinary environmental conditions in the American community, generally, is ample for the purposes of differentiation. This is not to say, arbitrarily or dogmatically, that there may not be some persons within the total population, whose ability to handle lead, physiologically, has been impaired in some significant manner. Such persons must, indeed, be few, and there is little reason to fear that any such persons would be affected adversely by the general levels of environmental exposure to lead that are under discussion in this statement. There are still occasional sources of exposure to lead in the modern American community, that need to be eliminated or controlled effectively, in order to prevent the occurrence of lead poisoning within the general population, notably among young children. Such cases, however, have no relationship in their etiology to the prevailing or imminent levels of the general environmental exposure to air-borne lead.

TABLE I

The ICRP* Lung Dynamics Model** predicts the following for particles of lead sesquioxide as defined below:

Measured mean diameter = 0.05 micron
Geometric standard deviation = 1.6***
Approximate density = 9
Count median aerodynamic diameter ≅ 0.15 micron
Mass median aerodynamic diameter ≅ 0.29 micron

Predicted Deposition	% Of That Inhaled	Predicted Clearance (Site)	(Half-time)	% Of That Inhaled
Naso-pharyngeal	7.0	Blood	4 min.	0.7
		G.I. Tract	4 min.	6.3
Tracheo-bronchial	8.0	Blood	10 min.	0.8
		G.I. Tract	10 min.	7.2
Pulmonary	40.0	G.I. Tract	24 hr.	16.0
		G.I. Tract	90 day	16.0
		Lymph -blood	90 day	2.0
		Blood	90 day	6.0
Total Deposition	55.0			
% In Exhaled Air	45.0			

at equilibrium 9.5% is cleared to blood
45.5% is cleared to G.I. tract

* International Commission for Radiation Protection.

** Developed by Task Group on Lung Dynamics for Committee II as published in Health Physics. Vol. 12, No. 2, pp. 173-208, 1966.

*** The model assumes a larger geometric standard deviation. For this particle size, the model would thus tend to overestimate deposition.