

KETTERING LABORATORY
EDEN AND BETHESDA AVENUES
CINCINNATI, OHIO 45219

July 13, 1967

Dr. Robert J.M. Horton
Health Effects Research Program
Public Health Service
5008 Federal Office Bldg.
Cincinnati, Ohio 45202.

Dear Dr. Horton:

We have discussed your letter of June 20, and agree that there is much to recommend a survey of the "tri-city" type. To clarify thinking on this point, however, we should indicate that we are dealing here with several questions which are related and yet deserving of precise and specific answers. It is useful to comment briefly on these questions:

- 1) To what extent is atmospheric lead responsible for body burdens of lead in persons living in certain environments?
- 2) How accurate is the determination of blood lead in estimating soft tissue lead or whole body lead?
- 3) What is the progressive year-to-year pattern of lead levels in urban populations and atmospheres?
- 4) What is the minimum body burden of lead which constitutes a hazard to health?

Question number 4 is outside the scope of this discussion because it would best be conducted on certain industrial groups known to be exposed to air concentrations of lead which are considerably above ambient urban levels.

Question number 2 reflects the uncertainty that blood lead levels accurately reflect the body burden (or soft tissue burden) of lead. We have already discussed with pathologists the feasibility of obtaining fresh body tissues from persons dying accidentally but who had previously been in good health. Appropriate bone and soft tissue lead assays relating lead concentrations to those in the peripheral blood have been proposed. There is a possibility that this cadaver study might be funded from a different source; however, discussions have been only tentative.

There remain, then, two principal questions: one concerned with trends of blood and air lead concentrations and the other which examines the relationship between air concentration of lead and tissue lead levels.

*is has been done
adequately, but
not strictly
relevant because of
the intermittent
character of the
exposure. The effect
of the time factor
upon the accuracy
of the data is
not with quantitative
can be approximately*

Of these, the first represents a re-survey of ambient air levels and populations previously examined. The validity of such work would be increased by maintaining insofar as possible the exact conditions observed in 1962. Ideally, persons surveyed in 1962 would be located and re-tested providing their location of residence or occupation had not changed during the interim.

With respect to correlations between ambient air lead concentrations and blood lead levels, we propose that a somewhat more detailed study be conducted in specific areas. Air sampling should be truly representative of those persons being studied. This is accomplished by the use of neighborhood sampling (blood and air) as opposed to more general regional investigation.

Primary consideration will be given to women in the study because occupational factors are less important and because relatively more time is spent by women in a single neighborhood. Commuters and people in industrial settings are less suitable if we are attempting to establish a correlation between lead body burdens and ambient urban lead concentrations.

The question of adding additional cities to those previously included in the study has been raised. We believe that a detailed study should be carried out only in Cincinnati and Los Angeles. Spot evaluations might also be made, however, in Philadelphia, Chicago and New York to confirm the general applicability of the detailed work and to determine the present status of lead-in-air and lead-in-blood concentrations in these large urban areas.

We also believe that information derived from the National Air Sampling Network may be useful in identifying several communities in which consistently low lead-in-air values provide a low end of the curve for correlation studies. While the measured levels are not comparable on an absolute basis with those which may be determined by the Laboratory, we at least know that levels approximating 0.1 microgram/m³ are consistently recorded in Cedar Rapids, Iowa; Massena, New York; St. Petersburg, Florida; Cheyene, Wyoming; and Helena, Montana. These levels are lower than the anticipated rural mean. Accordingly, there is much to recommend a small study in one or more of these areas, providing that the low lead-in-air levels are confirmed and determined continuously by a standard method.

We have determined blood lead levels in truly rural areas west of Cincinnati near the Indiana line. On the basis of our findings, it would be appropriate to study air and excretory lead levels in this community as a part of the Cincinnati survey. The feasibility of studying the inhabitants of rural religious communities has also been examined. There is no reason why this cannot be done, but it is probably best not to incorporate this work in the initial study.

A matter deserving special consideration is an evaluation of the extent to which lead in food and drink may account for body lead or differences in body lead of dissimilar populations. The tri-city study made no attempt to examine this variable which must be considered if we are to attempt a blood-air lead correlation. It is essential to identify the extent to which lead in ingested food and drink is responsible for any variations in blood lead which may be encountered.

Recognizing the difficulties associated with collections of duplicate samples of food and beverages, we feel that it is important to incorporate a fecal and urinary assay program in the study. Until this (or food assays) are done, we shall remain unable to present conclusive evidence that the cause of biological variations in lead levels is a specific reflection of lead in the atmosphere. There are obvious difficulties in the collection of excretory samples from neighborhood populations, but with suitable instruction and orientation this hopefully can be accomplished with good accuracy.

We feel very strongly that a tight experimental design is fundamental to the appropriate conduct of this work. Discussions have been held with Dr. John Varady of the University Computer Center, whose group is prepared to provide statistical consultation and comprehensive data management and analysis service.

To develop a feeling for the magnitude of this project, we summarize below an estimate of the sampling patterns and the volume of analytical work:

Stations

Cincinnati	-	10, including rural
Los Angeles	-	6 - 8
Philadelphia	-	2
Chicago	-	1 or 2
New York	-	1 or 2
NASN low-lead sites	-	2

Air Sampling

24 stations x 56 weeks x 3 filters/ week = 4,032 air samples.

(It is possible that a 2 x/week filter change would be adequate. It is also possible that pooling of aerometric analyses would represent certain economies of effort without significant loss of data. On the other hand, taped sequential samples should be used selectively and limited studies of particle size are warranted.)

Blood Sampling

20 geographic groups of 50 people each = 1000 samples
10 occupational groups of 50 people each = 500 samples

Metabolic Sampling

6 groups of 10 persons x 10 days x 2 excretory samples/person-day = 1200 samples

Cadaver Study

24 cadavers x 25 samples/cadaver = 600 samples
(4 cadavers in each of 6 decades of life)

We should like to comment briefly on the points raised in the minutes enclosed with your letter.

Revised Minutes - 14 March 1967

1. We agree that the three city pattern is useful and propose that it be repeated in a modified version.
2. The study should be initiated as soon as possible after detailed planning has been concluded. This is particularly important inasmuch as sequential sampling and analysis are contemplated. Subsequent studies will depend upon the initial findings, but to a great extent the nature of the possible subsequent studies must be established before any data are collected.
3. We propose that for 1967-68, Cincinnati (including at least one rural station) and Los Angeles be studied. Two low-lead sites identified by the NASN are proposed to establish correlations at the low end of the scale. While it will become necessary to confirm that general inferences can be made from specific areas, the immediate need is for reliable and specific local information. This is better achieved by meticulous and repeated observations in related controlled situations than by more general surveys. Stations in Philadelphia, Chicago, and New York are recommended to detect trends and validate basic correlations.
4. Ten survey sites in southwestern Ohio and 6 to 8 in Los Angeles are proposed. This will provide ample contrast and specific local information. Two additional low-level sites identified by NASN are recommended to extend the low range.

5. Pooling of results from a given station is permissible since integrated lead exposures are desired. The extent of the pooling remains open to discussion. Limited tape sampling and particle sizing is warranted, but certainly not on a continuous basis.

6. We agree that no change in analytical methods is advisable and that urine leads should be omitted. It may be worthwhile considering an investigation of gas chromatographic assays of lead as a chelate in order to establish the accuracy and precision of this highly sensitive technique.

7 and 8. While the use of selected population groups is recommended, we are not fully enthusiastic about police officers. The problem is that they move about a great deal and live and work in varying places. We believe that population groups living in stable neighborhoods represent a more suitable source of study groups. Ideally air sampling should be conducted in the immediate neighborhood of persons sampled. We have approached neighborhood groups in both urban and rural communities and have obtained good cooperation. We have also conducted preliminary talks with members of religious communities and find no administrative bar to sampling air and blood representative of such communities.

The importance of fecal surveys is again emphasized. While it is not necessary that all participants be on a collection regimen, it is important that we eventually document that alimentary lead is not responsible for any variability noted.

9. On the basis of the Three City Study, a detailed biostatistical framework should be prepared for the projected study.

10. Continuous quality control is central to the entire study.

May 31, 1967

1. A 13 - 14 month period is suitable; however, the decision to discard certain data should be made before those data are collected.

2. We propose that limited serial sampling be performed on members of the study groups. While previous studies show no seasonal variation, serial samples would confirm this observation. They would also tend to establish more precisely the true level of blood lead in a given population.

3. We agree that blood levels of $50 \mu/100 \text{ g}$ deserve prompt re-check and investigation as warranted.

4. Children should be excluded.

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5. We suggest that SALA not be investigated in the survey. This may possibly be a valid measure of one biological effect of lead, but we are not looking for biological effects of lead in this survey. If we were, we would recommend starting by investigating persons known to be exposed to relative high levels of environmental lead.

6. We agree that newcomers should be excluded. We are looking for persons who reflect the environment which is being measured and to which they are exposed. In pilot studies we have arbitrarily used 5 years local residence as a requirement for inclusion. In stabile neighborhoods this is not difficult.

7. The repeated reference to quality control is warranted. Quality control specimens should not be identifiable by persons performing the assay. We agree that 20 ml of blood is desirable; however it is not always convenient. For this reason we have suggested preliminary studies of gas chromatographic techniques. The proposed study is not the place to introduce new analytical methods as a primary tool. However, the usefulness of this technique as a check and an eventual method should be considered, and this is an appropriate time to do so.

In response to the request for a description of a quality control plan, the following outline may be useful:

a) 30 - 40 tubes of blood, each containing 12 - 15 ml, are filled in rapid succession by means of a doubled-needled plastic tube, one end of which is in the ante-cubital vein of a paid donor. The usual blood donor represents a blood level close to the anticipated mean. From a known high-lead patient representing a level of approximately 50 - 60 $\mu\text{g}/100 \text{ g}$ a similar series of tubes is obtained. We have not found that significant hemodilution occurs during the few minutes that 30 - 40 samples are drawn from a single subject. The samples are stored by freezing.

b) At suitable intervals a control specimen is withdrawn from storage, given a label which cannot be distinguished from the study group labels, and introduced into the general sample load being presented to the analytical group. Specifically: the control is not marked as such, its presence in a batch of tubes is not known to the technicians or laboratory supervisor, and it arrives at the laboratory in the conventional manner, i.e., it is not handed to someone while all other tubes come air parcel post.

c) Tubes are available to other laboratories for cross-checking.

d) A single individual of the department is responsible for the entire control tube program. A prime responsibility will be to assure that the "secret" nature of the program is maintained.

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9. Cross-checking to determine comparability between original and new studies is appropriate.

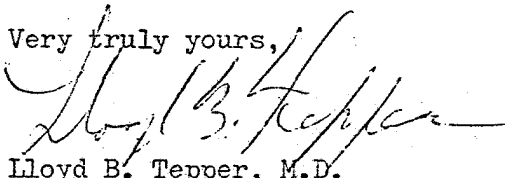
10. We have not discussed in any great detail the advantages of cooperation with either Dr. Vigliani of Milan or Dr. Petrovic of Belgrade. Both are established investigators and have staffs adequate for the conduct of air and blood sampling programs. They, in addition, have access to populations with relatively high blood lead levels, although the source of the absorbed lead is not entirely clear.

The source of the high atmospheric lead in these communities is presumably motor fuel, although gasoline consumption and lead content are relatively low.

After consultation with our epidemiological advisers, we will consider the way in which we might invite Dr. Vigliani or Dr. Petrovic to submit a proposal to us so that an efficient integrated survey can be accomplished. The sponsors of this entire project will obviously be kept informed of extensions in this direction.

We believe that a study can be developed which will provide specific answers to questions pertaining to lead in the atmosphere. We look forward to our discussions with you next week with respect to efforts in this direction.

Very truly yours,



Lloyd B. Tepper, M.D.
Associate Director

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