Reports

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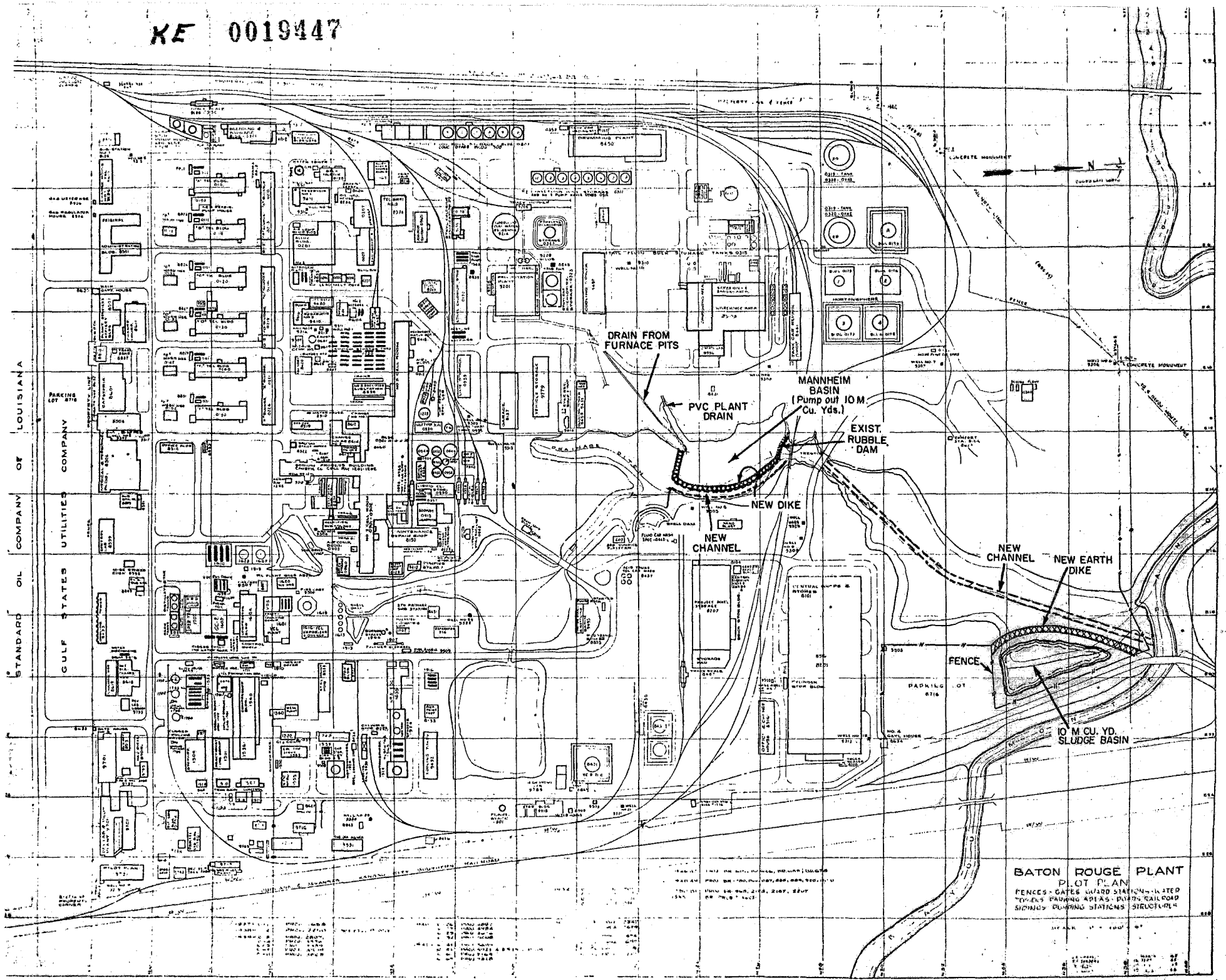
Papers on

Lead

KE 0019447

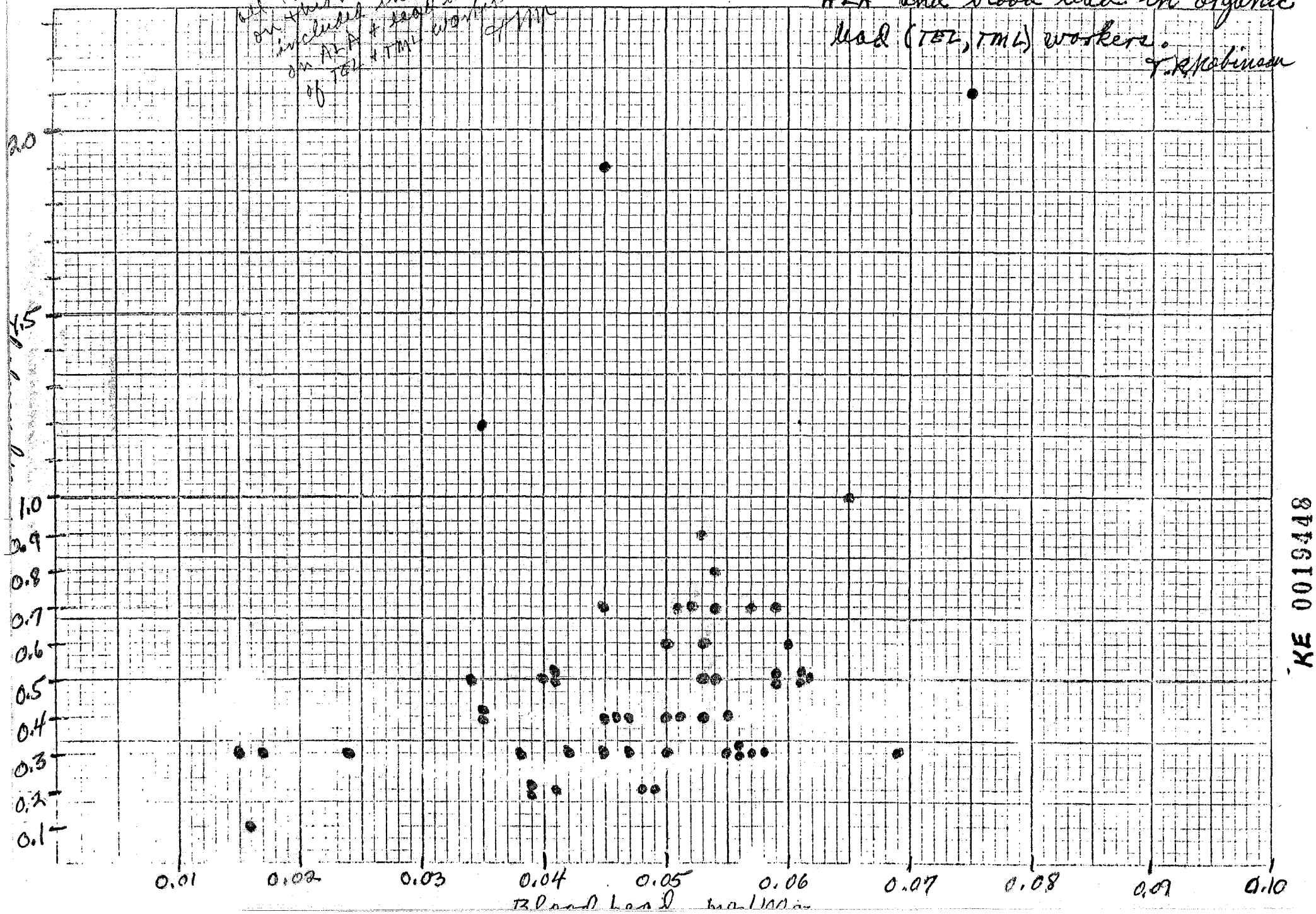

DRAIN FROM FURNACE PITS
PVC PLANT DRAIN
MANNHEIM BASIN (Pump out 10 M. Cu. Yds.)
EXIST. RUBBLE DAM
NEW DIKE
NEW CHANNEL
NEW CHANNEL
NEW EARTH DIKE
FENCE
10 M CU. YD. SLUDGE BASIN
DRAINAGE DITCH
STANDARD OIL COMPANY OF LOUISIANA
GULF STATES UTILITIES COMPANY
BATON ROUGE PLANT
PLOT PLAN

Dr. Kehoe –
This represents
all the data I have
on this matter – this is not
included in the paper
on ALA + lead in urine
of TEL + TML workers –

9/11/70

Correlation between urinary ALA and blood lead in organic lead (TEL, TML) workers.

T. K. Robinson



KE 0019448

Delta-Aminolevulinic Acid (ALA) and Lead in Urine of Workers Exposed to Organic Lead in the Form of Tetraethyllead (TEL) and Tetramethyllead (TML).

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Synopsis-Abstract

Delta-aminolevulinic acid (ALA) and lead were measured in the urine of workers exposed to organic lead in the form of tetraethyllead (TEL) and tetramethyllead (TML). The levels of ALA and lead in urine were found to have a relatively low positive correlation of $r=0.33$. These results are qualitatively similar to, but may be quantitatively different from, results reported by others for persons exposed to inorganic forms of lead. The mechanism through which the absorbed organic lead exerts its effect on urinary ALA is not indicated by this study. Urinary ALA values were found to be significantly less sensitive than urinary lead values as an indication of increased absorption of organic lead in the form of TEL and TML.

Elevation of the delta-aminolevulinic acid (ALA) level in urine has been reported to be a sensitive and, except for certain rare disorders of porphyrin metabolism, specific indication of increased absorption of lead[1,2]. The elevation is thought to result from a partial inhibition by lead of the conversion of ALA into porphobilinogen as one of the steps in the normal biosynthesis of hemoglobin. Such an elevation is an indication of a biological response to the absorbed material.

The usual clinical picture associated with intoxication due to inorganic lead[3] is quite different from that produced by organic lead in the form of tetraethyllead (TEL)[4]. The biochemical mechanisms underlying these differences are not understood. The reports that have been published concerning the effect of lead on urinary ALA levels have dealt with exposures to inorganic forms of lead. An investigation of the possible effects of absorption of an organic form of lead upon urinary ALA levels was considered to be of interest.

Materials and Methods

Subjects---One hundred twenty-six adult males of various ages and lengths of service, all working as operators or maintenance men in an area of production of lead alkyl antiknock compounds, provided the specimens of urine used in this study. Most of these men have a relatively much greater potential for occupational exposure to organic lead in the form of tetraethyllead (TEL) and tetramethyllead (TML) than to inorganic forms of

lead. Exposures must be considered to be to a mixture of TEL and TML, with the relative amounts of each component being variable and unknown for a given individual. The subjects were seen as part of a routine program of medical surveillance of employees working in this area of production. None of the subjects were clinically ill and none were on any type of "deleading" therapy.

Urine Specimens.---Each urine specimen consisted of a single voiding of 75 ml or more obtained at some time during the employee's normal working day. Most of the specimens were obtained from those workers thought to have the greatest potential for increased absorption of organic lead. A few specimens were obtained from subjects whose work was thought to offer relatively little opportunity for occupational exposure to lead in any form. A small portion (about 2 ml) of each specimen was set aside for determination of ALA concentration and was stored at 5°F (-15°C) until analysis. No measurement or adjustment of urinary pH was done prior to storage. The remainder of each specimen was used for determination of lead concentration. A total of 280 urine specimens were analyzed for both ALA and lead.

Analyses.---All ALA determinations were done in the clinical laboratory of the plant medical facility, using the modification by Davis et al[5] of the method of Mauzerall and Granick[6]. Disposable ion-exchange chromatographic columns and reagents were obtained commercially (Bio-Rad

Laboratories, Richmond, California). Standards were run with each group of specimens analyzed. It should be recognized that the lower ("normal") values for urinary ALA indicated by the method used are only in part (10-20%) due to ALA, with the balance presumably being due to a residue of amino ketones and glucosamine[6]. However, this method has been shown to be specific for elevated values of ALA found in subjects having a disorder of porphyrin metabolism[1,6], and in subjects having excessive absorption of inorganic lead[1].

All lead determinations were done by the Analytical Section of R & D Services at Ethyl's Baton Rouge plant by a modification (Ethyl Analytical Procedure No. 138, Baton Rouge) of the dithiazone method of Snyder[7]. This method determines total lead in the urine.

Results

The values obtained in this study for ALA and lead in urine are shown in Figure 1. The expected (normal) range of each component for persons not occupationally exposed to lead are indicated. For purposes of calculation, the lower (normal) values for ALA were used as if they were due entirely to ALA; the resulting correlation coefficient is $r = 0.33$.

Figure 2 shows the urinary ALA and lead values over time for each of six workers who have been followed for a number of months. Urinary ALA and lead are seen to vary concommitantly over time in these workers. Of the men studied in this manner, one (Subject #70, Figure 2) shows an apparent

quantitative difference from the others in his urinary ALA-lead relationships.

Discussion

The degree of dispersion of the results reported here is such that no single line or curve is thought to be justified as portraying the relationship between ALA and lead in the urine of these workers. It is not clear whether this dispersion is primarily due to innate variability of response of individuals to absorbed organic lead, to differences in the composition of the TEL-TML mixture to which individuals were exposed, to differences in the exposure / no exposure time relationships, to differences in intervals between exposure and sampling, or to other possible variable factors. Because of this degree of dispersion, precise quantitative comparison of these results with the results others have reported for exposures involving inorganic lead[1,8,9,10] cannot be made. However, comparison of such results by simple inspection (Figure 3) suggests that a given elevation of urinary lead excretion probably is associated with a lower level of urinary ALA excretion when exposure is to organic lead (TEL,TML) than when exposure is to inorganic lead. It is not clear whether this difference might be related primarily to differences in circumstances of exposure or to differences in metabolism (biotransformation) of the different forms of lead to which exposure occurred.

In vitro and in vivo studies by Cremer[11] and in vivo studies by

Bolanowska[12] suggest that TEL is converted, at least in part, in the body to triethyllead and that this latter form of lead produces a disturbance in central nervous system function similar to that observed in intoxication due to TEL. Unconfirmed results by Bolanowska indicate that triethyllead may be excreted as such in urine and feces quite slowly and without evidence of further degradation by the body. A portion of Bolanowska's work suggests that some part (less than 20%) of absorbed TEL may be converted directly to inorganic lead by the body. This portion of lead presumably would behave in a manner physiologically the same as lead derived from inorganic lead exposures, including effects on porphyrin metabolism and urinary ALA excretion. This suggests also that the urine of persons who have absorbed TEL contains organic as well as inorganic lead.

In vivo and in vitro studies by Cremer and Calloway[13] suggest that TML may undergo a relatively slow conversion in the body to (the more toxic) trimethyllead. No evidence has been reported to indicate whether or not some portion of absorbed TML might be converted directly to inorganic lead within the body. The excretion product(s) of TML is (are) not known.

There have been no studies reported to indicate what effect, if any, triethyllead or trimethyllead per se might have on porphyrin metabolism and hence on urinary ALA excretion.

It is impossible at present, therefore, to assess the relative importance of TEL and TML (and possible metabolites of these compounds:

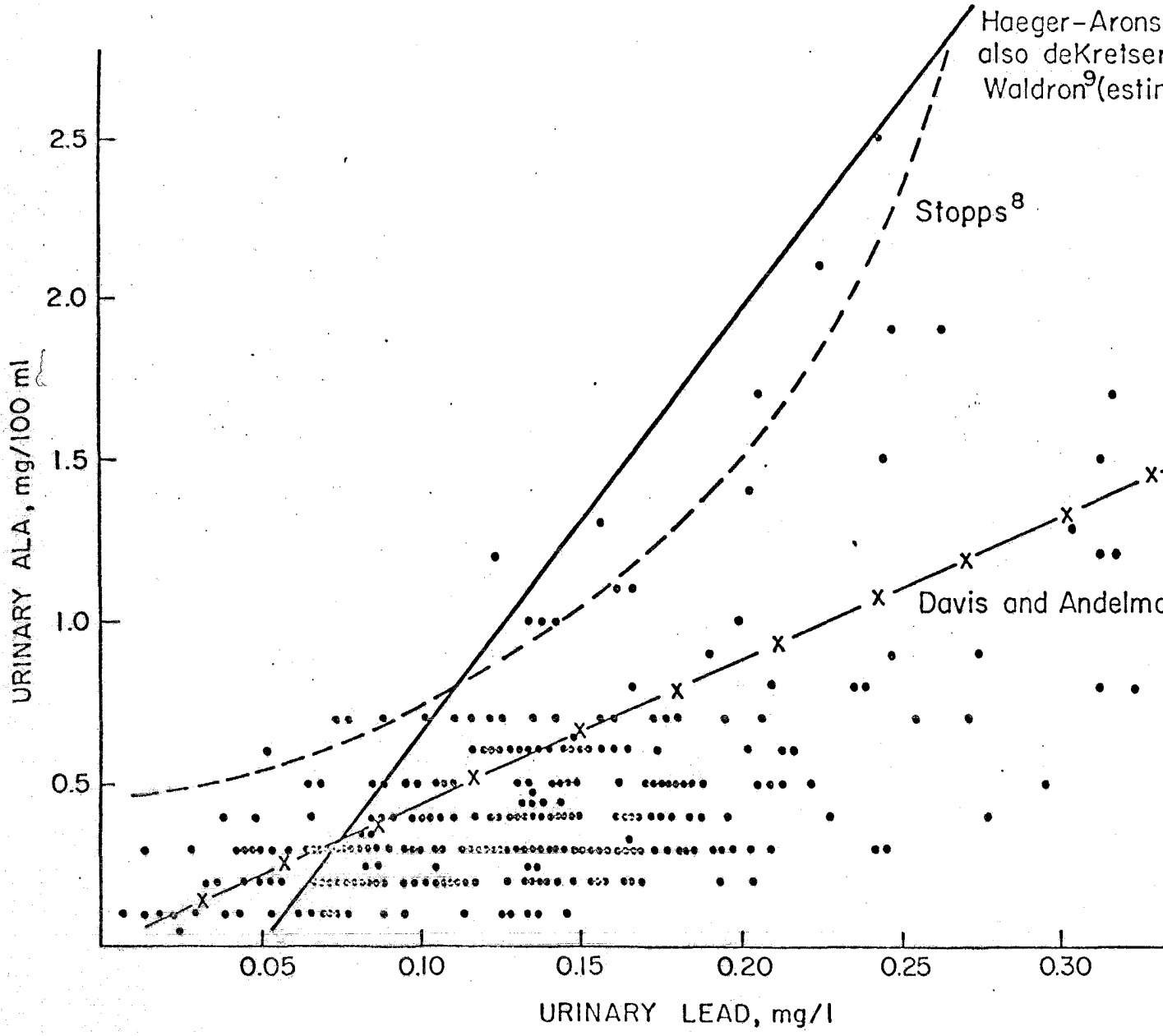

Figure 3. Comparison of Reported Urinary ALA : Lead Relationships for Exposure
Inorganic Lead With Results of Present Study Involving Organic Lead (TEL, TM

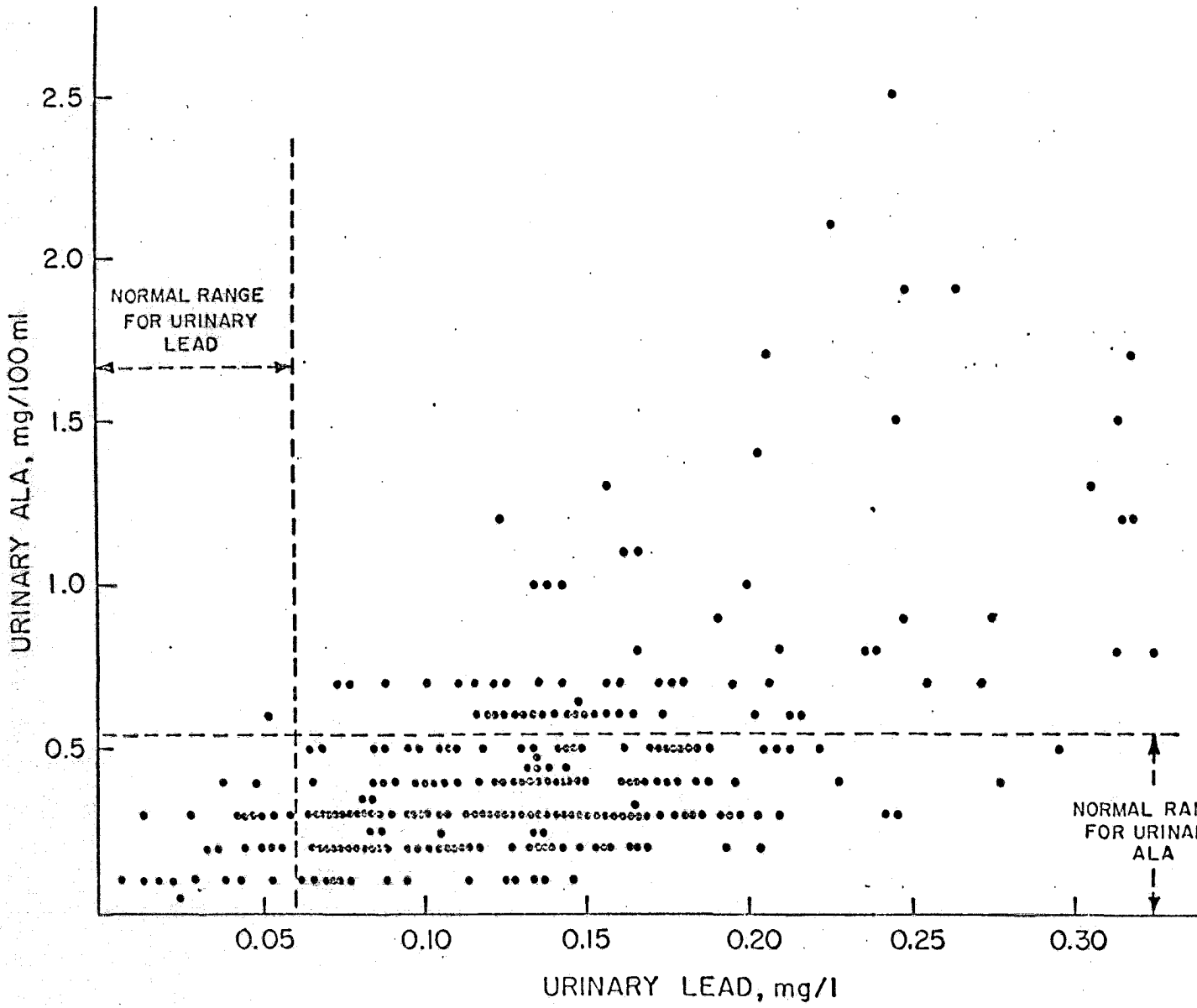

Figure 1. ALA and Lead in the Urine of Organic Lead (TEL, TML) Workers.

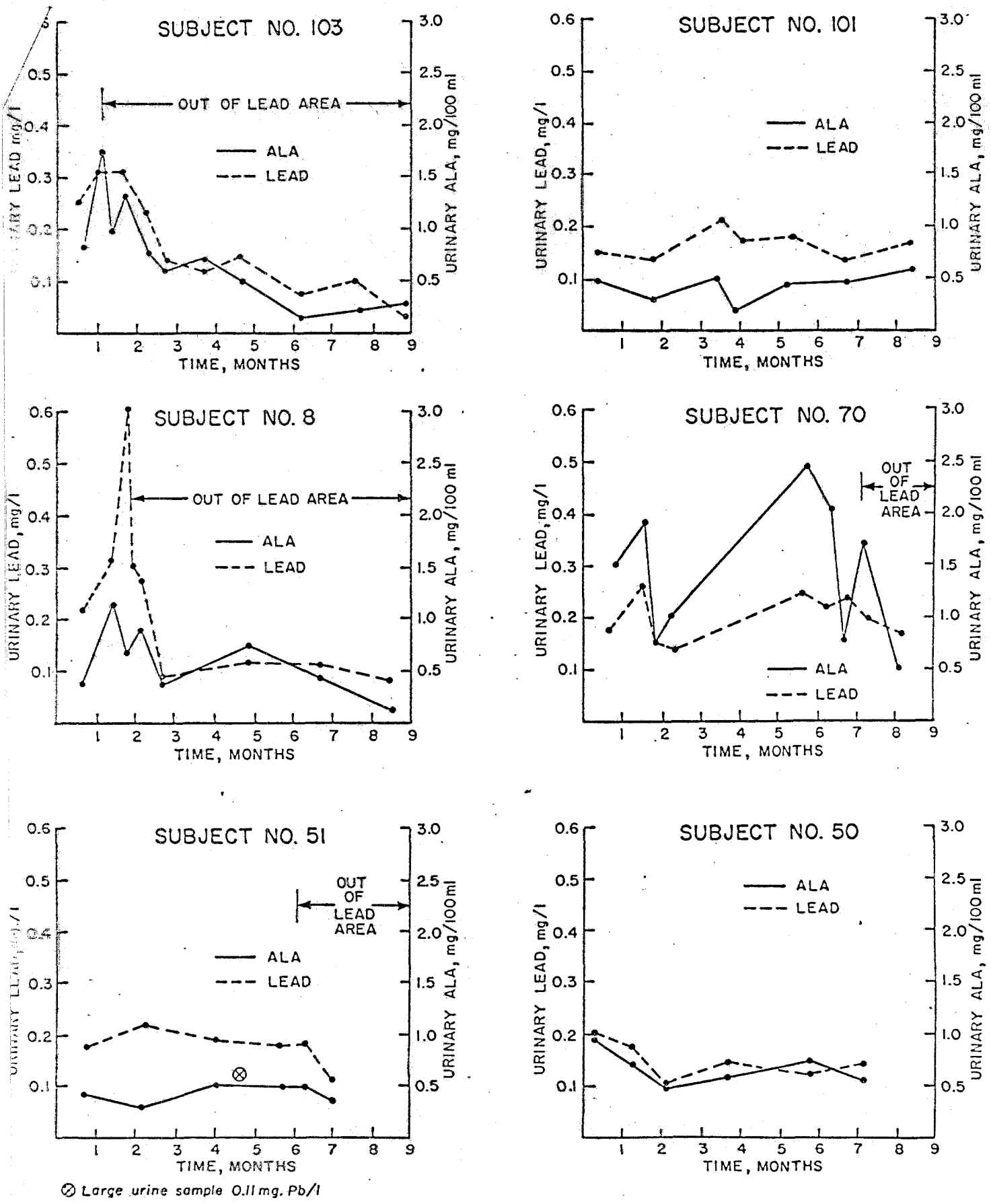

Figure 2. Trends in Urinary ALA and Lead Levels Over Time in Certain Organic Lead (TEL, TML) Workers.

triethyllead, trimethyllead and inorganic lead) in producing the deviations from normal of urinary ALA values observed in the present study. Further investigation must be done if the roles of the various compounds mentioned are to be understood.

An increase in urinary excretion of porphyrins has not been noted following exposure to TEL[4], in contrast to the elevation found following absorption of inorganic lead. The results of the present study suggest that porphyrin metabolism is affected at the ALA level (i.e., prior to the formation of porphyrins) by absorption of one or the other (or perhaps both) of the forms of organic lead (TEL,TML) involved in this study.

Subject #70, whose urinary ALA:lead relationship seems to differ from the other subjects in this study (Figure 2), works in the lead recovery (furnaces) area of the plant. His job may entail a greater potential for exposure to inorganic lead than do other job assignments in the organic lead production area. This subject's urinary ALA:lead pattern is quantitatively quite similar to those reported by others for workers exposed to inorganic lead[1,8,9]. None of the other furnace workers seen during the course of the present study exhibited a significant elevation of either urinary lead or urinary ALA and thus do not furnish information to evaluate this point more definitively.

Determination of ALA in urine has been considered by some authors to be of considerable value in the routine monitoring of workers exposed to

inorganic lead[1,14,15]. It has been suggested that determination of urinary ALA, a measurement of biological response, should replace determination of lead in blood or urine in the monitoring of workers exposed to inorganic lead. This probably would be unwise in most circumstances. Blood and urinary lead values not only specifically identify and estimate the magnitude of the absorption of lead by individuals but also, when collected systematically over a period of time, can be of great utility in the assessment of the hygienic significance of changes in work procedures and practices, equipment changes, etc. ALA and lead determinations supply different types of information, both of which are needed for the proper evaluation of many situations. The one is complimentary to, but cannot replace, the other.

The present study indicates that urinary ALA determinations are of relatively limited value in a monitoring program where the potential for exposure is primarily to organic lead (TEL,TML), due to the relative insensitivity of this test under such circumstances. As can be seen in the group results (Figure 1) and in results for individuals (Figure 2, Subject #51 and #101), levels of urinary lead shown by long experience to indicate the desirability for reduction of exposure to lead (i.e., a consistent urinary lead level of 0.18 mg/l or more) may be associated with levels of urinary ALA that are within normal limits. Until and unless an extensive background of clinical experience confirms the safety of the use of urinary ALA levels for

the medical control of workers exposed to organic lead (TEL,TML), the present standards, based upon urinary lead values, should continue to be used in such control programs. The determination of lead in urine must still be considered to be the most useful laboratory tool in the routine medical monitoring of workers having a potential for exposure to organic lead in the form of TEL and TML.

As a relatively early objective indication of a response to the increased absorption of lead, consideration should be given to the determination of urinary ALA as a part of the medical monitoring of workers having a potential for exposure to lead in any form. Information of this type should be of value in long term clinical and epidemiological studies and may be useful in the evaluation of such additional indications of biological response as may be developed in the future.

In summary, the present study shows that absorption of organic lead in the form of TEL and TML, as indicated by increased urinary lead levels, is associated with an increase in urinary ALA levels. The mechanism through which this effect is produced is not revealed in this study. Urinary ALA does not appear to be as sensitive an indicator of absorption of TEL and TML as is urinary lead and is thus of ancillary, rather than primary, value in the routine medical monitoring of workers having potential for exposure to these forms of organic lead.

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Legend for Illustrations

1. ALA and Lead in the Urine of Organic Lead (TEL,TML) Workers.

2. Trends in Urinary ALA and Lead Levels Over Time in Certain Organic Lead (TEL,TML) Workers.

3. Comparison of Reported Urinary ALA:Lead Relationships for Exposures to Inorganic Lead With Results of Present Study Involving Organic Lead (TEL,TML).