

CORRESPONDENCE, ETC. AND COMMENTS RE.
REPORT OF NATIONAL ACADEMY OF SCIENCES
on LEAD IN AIR

N13349

KE 0012839

November 30, 1970

Bertram D. Dinman, M.D.
School of Public Health
University of Michigan
Ann Arbor, Michigan 48104

Dear Bert:

I enclose herewith my comments to you ^{about the draft of the report} (not to any other person) concerning the first draft of the report of your Panel. I have struggled manfully with the completion of my comments during this week-end holiday, for I simply cannot, right now, spend any longer time on it. I have not entirely succeeded, and what I have done has not been quite as I was instructed by Dr. Marshall. Rather, I have said certain things to her, and I enclose a copy of these remarks.

On the other hand, I have considered it necessary to acquaint you with the means by which I have arrived at my formal comments, since otherwise they might seem not to be entirely valid. My comments to you have been hurried, but I believe you will disregard their faults, in favor of examining them for their worth in relation to this problem. I could wish that I had more time at my disposal, for the problem of your Panel is a difficult one, which you, as well as I and others, must approach without all of the facts required to prove the correctness of the position taken. For example, the lack of precise information about the "body burden" of adults, generally; and the incomplete information as to the clearance of inhaled lead from all parts of the respiratory tract, especially the alveolar bed. It is easy not to be biased (that is opinionated) when all of the facts are in. Since they are not, we have views, impressions and yes! conclusions, arrived at for reasons that differ, as to their sources, from those that stem from comprehensive physiological information. I have attempted therefore to give you some of my views, and this could hardly be done without disclosing the fact that what I have said in some instances came almost uniquely from me. To this extent, you can take them or leave them, without too much difficulty, and I shall not feel that I have failed to inject the element of thought and interpretation into my review. Actually, there is no matter of profound importance to the population of this country (or of the world) on which we have the facts in such form that only one interpretation can be made of them. It is at this point, that intelligence, imagination and motivation enter inevitably into our conclusions. And so, I believe, it will always be.

I conclude this letter by saying that Chapter 3 should be rewritten to clarify the issues in this situation, and to bring the available facts to bear upon the matters at issue.

Sincerely yours,

enclosures

RAK:wb

Robert A. Kehoe, M.D.
Professor Emeritus of
Occupational Medicine

KE 0012340

COMMENTS

Chapter 1

The statement at the top of page 13, beginning on the previous page, in which references 13, 14 and 23 are provided as documentation, should be deleted and the references eliminated. The regulations referred to as being "promulgated" by the USPHS were never put into effect, as such, for the reason that Ethyl Corporation and I agreed to assume the responsibility for doing the necessary experimental work at the cost to the Corporation and also to handle the problems properly. Keenan's chapter is adequate, I think, and should not be spoiled by this comment which concerns itself with matters which he could not know about. This mistaken idea is still believed by many people in the Service and in the government. The facts of the matter are that the regulations as proposed in Bulletin 163 were almost entirely irrelevant. They were proposed by the group of men - a committee of experts appointed by Hugh Cummings - who knew a great deal about the methods suggested officially for dealing with the problems in the trades and industries concerned with inorganic lead. They were, for the most part, quite irrelevant to the special characteristics of the alkyl lead compounds. Fortunately, they had no legal standing and so could be followed "in spirit and purpose." Obviously, since the industry concerned, was under fire at that time, I did not say anything about the matter publicly, and have never attempted to do so since. At the time these regulations were proposed, no one knew how to prevent difficulties. We learned by experiment and experience, and it is entirely correct to say that all of the methods developed to enable tetraethyllead and Ethyl Fluid to be manufactured safely were initiated and put to work by and entirely within the industry. The manner of setting up the mixing with gasoline, likewise, was developed by the industry and imposed upon the petroleum industry through actual contracts whereby they bound themselves to accept the acts and regulations of Ethyl Corporation in matters of procedure and safety.

COMMENTS

The one thing new and important which appeared in these regulations concerned the matter of supplying Ethyl Fluid to the petroleum industry and introducing the product into gasoline. In order to obtain official sanction for discarding utterly the initial procedure of supplying Ethyl Fluid in small containers to service stations, from which in an ingenious piece of equipment, it was metered into the automobile tanks with gasoline, I requested Dr. Cummings to include in the recommended regulations, a statement that the mixing must be done only where large amounts of gasoline were stored. This resulted in the policy of licensing refineries exclusively to perform these operations, and thereby we eliminated the exposure to tetraethyllead on the part of tens of thousands of service station personnel.

Since Ethyl Corporation performed its job well and in silence, very few people knew anything about these matters, except that trouble from this source disappeared completely. It was assumed, therefore, that the USPHS had handled the matter effectively.

It is high time that this myth should be forgotten. I would not advise that any statement be made but that Keenan's sentence and the references be deleted.

CHAPTER 3

Page 1, line 5 of first paragraph - "Most" should be "much" in view of work done by superior methods of investigation within the past two decades.

Page 1, bottom paragraph, line 1 - To "Lead salts" should be added the "oxides". In this paragraph also, the statement should be made, despite the meager evidence, that "thus far, the problem in man has been dermatitis, rather than highly significant percutaneous absorption.

Page 2, bottom paragraph - It should be made clear that the absorption of tetraethyllead through the skin is of great significance - that it is capable of resulting in serious CNS symptoms which often lead to fatal results.

KE 0012342

COMMENTS

Page 3, line 6 of main paragraph - The word "excretion" should not be employed in dealing with the fecal "evacuation." Most of the lead is not "excreted" in the true sense, but rather is merely "en route" evacuation following ingestion. True excretion via the alimentary tract / is rarely more than three times that in the urine, and is often less than or only about equivalent to that in the urine (when the total excretion is small).

Page 3, sentence beginning on line 6 and extending into line 7, and the next 3 sentences - The use of the term "body burden" here is incorrect and misleading, since it was unknown. The factor here was the quantity actually accumulated as observed during the course of the experiments; this was approximately correct. The "net absorption" in these experiments varied (perhaps with the subject), but certainly with the quantity of lead available in the alimentary tract, up to as much as 14%, and as little as 5%, as the reference will show. The dosage (line 10) extended up to 3 mg. (Pb) per day in these experiments. Lead metabolism, under ordinary circumstances (normally chosen diet), has been investigated over periods of months or years in 20 subjects. This is the part of this investigation which bears, especially, on environmental exposure to lead, thereby providing a large body of relevant information, not otherwise available. Apparently, the importance of this information was not realized by the author, who failed to recognize the purposes and the implications of the approach to the normal metabolism of lead under ordinary environmental conditions.

Page 4, bottom paragraph, entire - Observations have been made on the metabolism of lead in man under the influence of both calcium and phosphorus (phosphate) alone and in combination, and also of Vitamins C and D. No significant effect is discernible, save for alterations in the output of water (urine), excepting in the case of Vitamin D. The statement that the retention of lead in the body of man is altered after the oral administration of calcium or phosphorous, or both, is not justified by the observed facts. Under ordinary circumstances, the metabolism of lead appears to be independent of both, within wide quantitative limits of both.

KE 0012843

COMMENTS

Page 5, sentence beginning in bottom line, relative to the Respiratory tract, and extending to page 6 - It may not properly be "assumed" that "lead deposited in the pulmonary alveolar bed," is absorbed directly into the blood stream. While the mechanisms of pulmonary alveolar clearance are subject to certain inferences, their actual quantitative significance, in relation to finely divided particles, especially the very small particles well under 0.1 micron in diameter, are not known and cannot be inferred. Only precise information of their behavior will suffice, and this has not been done (or at least is not recorded to have been done). Particles of minute dimensions (mean 0.05 micron, maximum 0.2) are exhaled, following inhalation, up to 50% (or more, dependent upon various factors). Calculations, as to absorption, therefore, must depend upon assumptions which may be in serious error. The question, from a practical viewpoint, which must be the present means of approach, arises as to whether the quantity absorbed, under specific conditions, is sufficient to demonstrate its significance, quantitatively, in the presence of absorption from the alimentary tract, in the form of a significant increase in the rate of the urinary excretion (which occurs as the first indication), and (later) in the elevation of the concentration of lead in the blood. The problem is confounded by the day to day and season by season variability of the absorption of lead from the alimentary tract - this variability being induced by the variability of the quantities of lead ingested from day to day with food and drink (which results from dietary choice), and renders impossible the detection of the relatively minute quantities which may have been cleared from the respiratory apparatus into the alimentary tract when the particles of lead were sufficiently small to have been trapped initially in the pulmonary alveolar bed.

The foregoing matters, from the practical viewpoint, were the "major value" of these experiments. Certainly their "major value" was not the fully expected finding that, when the inhaled particles were large, the gross increase in the presence of lead in the alimentary tract could be discerned. The latter matter relates

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primarily to occupational exposure to lead dusts, not to fume. The minute size of the particles emitted from the tail-pipe of automobiles, which continue to be airborne for prolonged periods of time, is the main problem of lead in the ordinary or ambient atmospheric environment.

Page 11, et seq. - Much of the discussion of the distribution of lead in the body of man, while not entirely incorrect, is irrelevant to the question of whether, under the ordinary conditions of life in the ordinary environment of life (excluding unusual or abnormal degrees of exposure to lead which can be ascertained; many are not), there is a progressive accumulation of lead in the body. Balance experiments (which are not, in the precise sense, strict balances) say that such accumulation does not occur to a significant extent. Observations on the body burden of cadavers appear to say that accumulation may occur. This is arguable, especially in terms of significance, and this is where the argument lies. The significance lies in the characteristics of the total body burden, and as to what proportion of it is physiologically active (or toxicologically active, if you will). This issue should be made clear in this report, and it is not.

The significance of the distribution of lead in the tissues and skeleton, (especially in the skeleton), is the crux of the matter, and while some of the facts in this regard are presented by the author, the problem is not. For example, the reference to/^{the}manner of expressing the concentration (bottom of page 11), and then stating that this can be made more nearly uniform by expressing it in terms of the ash, is wholly irrelevant, since, by so doing, the relationship of the lead in the organs to what remains after the destruction of the materials which may have combined with lead, only removes one further from the significant truth of the selective distribution of lead in the living body.

As to the distribution of lead in the body, according to the type and composition of the organs and tissues, of the body, the nature of the distribution in

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the intact organism (man), at present, is being inferred on the basis of the supposed equilibrium, (continuously being disturbed by continuing absorption), which exists between the blood (the cellular elements of which make it an organ similar to other organs, (or is it?), and all of the other vascular tissues of the normal body.

Page 12, bottom paragraph - In the discussion here, the author misses the point that the progressive accumulation of lead in the body of man, in association with the oral administration of lead, well above the ordinary environmental (which is represented by continuous absorption day and night and week-ends) is of totally different magnitude from that which results from the normal metabolic pattern of the individual within his ordinary environment. In the latter, the intake and output of lead are substantially equivalent, with an actually greater output than the intake, because, presumably, of the failure to measure the intake from the air. The fact that a considerably larger (two fold) intake of lead orally can yield accumulation is the whole point of these experiments, since this was not the case under ordinary environmental conditions. The evidence exists (unpublished) that there is some slight increase in the body burden of animals subjected to exposure to conditions roughly similar - possibly not - to those of man under normal conditions. The question, therefore, assuming for the moment (not necessarily true) that man behaves likewise, is whether this slight degree of retention will be significant in a lifetime. Here again, is where the discussion of essential matters should lie, and it is not evident that this is the issue of the author's discussion.

NOTE: Other points in the author's discussions of distribution are worthy of comment, but enough has been said above to indicate that this chapter should be rewritten, with a point of view toward the real issue of the metabolism of lead in man under normal or ordinary environmental conditions. The facts set forth by the author are rarely incorrect in the actual sense, but they are irrelevant to the issues which are the consideration of this Panel. A large proportion of the observations of

November 30, 1970

Louise H. Marshall, Ph.D.
BEAP Committee
National Research Council
2101 Constitution Avenue
Washington, D.C. 20418

Dear Doctor Marshall:

I am enclosing herewith certain comments which I have thought should be made about one part of the Report of the Panel on Lead, to the Committee on the Biologic Effects of Atmospheric Pollution. I have made only one other comment on a statement and three references in Chapter I-A, page 13, to Doctor Dinman only. A copy both of this letter and of my comments have gone to Dr. Dinman. I should tell you also that I telephoned Dr. Dinman at his home in Ann Arbor, charging the call to your telephone number, as you asked me to do, for the reason that I wished to say some relevant things to him, off the record, which I thought would be useful to the Panel.

As you will note, I have commented, almost entirely, on Chapter 3. I have read the entire Report, and I have little to say about the greater part of its contents. Several aspects of these contents are dealt with in a manner which seems to me to be adequate, or so nearly so, from my viewpoint, knowledge and experience, as to require no comment from me. Moreover, since I am up to my eyes in other editorial work, I have not undertaken to spend any more time on this Report than was required, during this long Thanksgiving holiday. However, there are defects in Chapter 3, which require me to speak if I am to serve this Panel in an honest and responsible manner. I have attempted to follow your instructions to remain anonymous, but in view of the very nature of the contents of Chapter 3, and the parts of it on which I have ventured to comment, however objectively, such may not be possible. Therefore, I have been much more explicit in my comments to Dr. Dinman.

I trust that I shall have assisted the panel as much as I can, despite the brevity of the time I have spent in my examination and comments, and I shall do my best to give proper time and attention to the final chapters, when they are forwarded to me.

Sincerely yours,

Robert A. Kehoe, M.D.
Professor Emeritus of
Occupational Medicine

RAK:wb
cc: Dr. Dinman

P.S. The volume on which I have made no notations has been mailed to you.

RAK

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COMMENTS

investigators are recited, and as a review of the entire field, the author has covered much indeed. However, he does not relate these to the issues, and one gathers that he does not see the real issues relating to the common environmental exposure of mankind (and of specific geographical representations of mankind).

Comments are also to be made in connection with 3. Excretion. These are omitted at this time, as are those required to deal with some statements and concepts in 4. Body Burden, because of the inavailability of time. This entire chapter should be rewritten (not discarded, but corrected and reorientated).

N13349.03

KE 0012346

REVIEW OF FIRST DRAFT OF REPORT OF PANEL
ON THE BIOLOGIC EFFECTS OF LEAD IN THE AMBIENT AIR

The critique of this reviewer is directed primarily to Chapter 3. The other chapters have presented the relevant information from the literature in a satisfactory manner, in so far as the knowledge and experience of this reviewer are competent to judge, and in its bearing upon the issues here concerned.

In Chapter 3, on the other hand, the difficulties of the task of assembling the pertinent physiological information concerning the so-called "normal" (normal to our time and geographical location) metabolism of lead are very great, and their interpretation, considering the lack of certain important facts, (the clearance of lead in various forms and states of subdivision from the respiratory tract, following their inhalation; and the inadequate direct information on the "normal" ^{burden} body), are even greater.

(a) Not all of the relevant information has been presented, and some of the interpretations of that presented have not been drawn as well as they might be, in the opinion of this reviewer.

(b) Conclusions as to the primary issues have not been drawn unequivocally, nor have the basis for uncertainties in important matters, been presented clearly.

(c) The basic issue (which is unique to this period of time) has not been stated or brought under discussion. That is the question of the significance of the quantitative characteristics of ^{the} metabolism of lead at the low level which characterizes normal or current, general environmental conditions of exposure. Is there, really, a quantitative aspect to the toxicology of lead, and if so, what is the evidence for and against this concept? Or is the current lay concept correct, that any quantity (or concentration) of lead in the body of man is bound, ultimately, to have some deleterious effect if we can learn how to discover it? Where is the point of differentiation, in terms of effective concentration, between what may be entirely harmless and what is somewhat harmful? In short, how can negative information be made useful in this and

other matters of like or similar kind?

It is the opinion of this reviewer that Chapter 3 should be rewritten. As a first draft, it is not to be condemned as bad, but rather as insufficiently oriented to the matters at issue. Thus, matters are dealt with lightly which require careful examination and discussion, while others, sometimes irrelevant, are given undue attention.

KE 0012350

NATIONAL RESEARCH COUNCIL

NATIONAL ACADEMY OF SCIENCES NATIONAL ACADEMY OF ENGINEERING

2101 CONSTITUTION AVENUE WASHINGTON, D.C. 20418

DIVISION OF MEDICAL SCIENCES

23 November 1970

Dr. Robert A. Kehoe
Department of Environmental Health
University of Cincinnati
Cincinnati, Ohio 45219

Dear Dr. Kehoe:

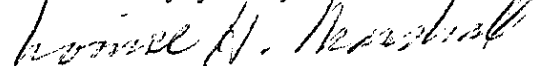
Enclosed is the first draft of the Panel on Lead's report to the Committee on Biologic Effects of Atmospheric Pollutants. The Associate Editor for this panel, Dr. Bertram Dinman, was happy to have you agree about two months ago to serve as an anonymous reviewer of this report.

The first draft is not entirely complete but we are sending it now because of NAPCA's tight schedule and the fact that the panel will meet on December 3 and 4 to apply the final touches. To be added to the report are Chapters 8, 9 and 10, covering the Appraisal of Impact, the Conclusions, and Summary and Recommendations for Research. It will not be possible at this time to determine whether the evidence justifies the conclusions which will have to wait until the final chapters are sent to you.

Also enclosed are guidelines for the reviewers. You will note that it would be a waste of time to concern yourself with details of format and stylistic conventions. We prefer to have suggested changes made on separate sheets of paper. Because changes from other reviewers will be coordinated by my office, we suggest that they be sent directly to me rather than to Dr. Dinman. My address and phone number are noted at the bottom of the guidelines. If time is too short to mail your suggestions so that they reach my office by December 2, please telephone them to me before that date.

Dr. Dinman suggests that as you review the draft you will make your comments in such a manner that they will not reveal your identity. The deadline for receipt of your comments, if they are to be of use to the panel, must be December 2. We appreciate very much your willingness to undertake this massive but very important task.

Sincerely yours,



Louise H. Marshall, Ph.D.
Professional Associate

P. S. Please do not hesitate to call Dr. Dinman (and charge the call to my number) or myself if we can be of any assistance.

LHM/th

N13349.05

Enclosures
cc: Dr. Dinman

KE 0012851

January 18, 1971

Dr. Louise R. Marshall
National Research Council
2101 Constitution Avenue
Washington, D.C. 20418

Re: BEAP Committee Report

Dear Doctor Marshall:

I have gone as far as I can, that is, as far as my available time will permit, in reviewing and discussing the part of the first draft of the Report of your Committee, which I considered to be most in need of attention - namely, the part written by Doctor Hammond, Chapter 3. It may be that what I have done will not be very useful, but I have spent a great deal of time in trying to clarify matters which seemed to need attention. I simply have not the time to do more just now, for I am far behind in editorial work which should have been completed weeks, if not months, ago.

The problem, in my opinion, is our lack of complete understanding of some of the physiological aspects of the situation presented by the contamination of the earth with lead, which began centuries ago and continues to the present time. On the other hand, our knowledge is very much greater than the mere search of the literature, much of which has lacked critical examination, has indicated, and it is this which I have undertaken to bring into the picture, as well as I can. Such a thing cannot be done by brief comments and critical remarks, or so it has seemed to me.

At any rate, I hope that what I have done will be of some help to your panel. I am sending to you two copies of the two types of comments which I have assembled. My purpose in doing so is to make sure that Dr. Dinman will receive a copy, for I fear that copies sent to him separately may not reach him before he leaves Ann Arbor for Washington.

I came to San Francisco some days ago, and have been working at this most of the time since I arrived. I must now send my handwritten material to my secretary to transcribe and forward to you. I hope that she will be able to get it to you promptly. You have her address and telephone number (that of my Cincinnati office), and I can be reached here at 1051 Francisco Street, San Francisco, California 94109. Our telephone is (415) 885-5159. Do not hesitate to call me if I can be of further assistance.

Cordially yours,

RAK:wb

Robert A. Kehoe, M.D.
Professor Emeritus of Occupational Medicine

Dictated but not read

KE 0012352

N13349.06

January 19, 1971

Bertram D. Dinman, M.D., Director
Institute of Environmental and Industrial Health
The University of Michigan
School of Public Health
Ann Arbor, Michigan 48104

Dear Bert:

I am sending a copy of my comments, which have been restricted to Chapter 3, of the first draft of your report, which I believe to be the part about which I can be of greatest assistance. Two copies have gone to Dr. Marshall so that if I miss you, through tardiness, you will find a copy in Washington.

What I have done is quite unorthodox, I believe, but to my way of thinking, it is the most useful job that I can do. At any rate, I hope it will be helpful in clarifying some of the matters which seem to me to be important.

Lucile and I are in California, and I must send my handwritten material to my secretary, Mrs. Bice, to transcribe and forward. I hope she will be able to do so promptly.

With kindest regards,

Sincerely,

Bob/wb

Robert A. Kehoe, M.D.
Professor Emeritus of
Occupational Medicine

RAK:wb

Dictated but not read

enclosure as stated

N13349.07

KE 0012353

NATIONAL RESEARCH COUNCIL

NATIONAL ACADEMY OF SCIENCES NATIONAL ACADEMY OF ENGINEERING

2101 CONSTITUTION AVENUE WASHINGTON, D.C. 20418

DIVISION OF MEDICAL SCIENCES

21 January 1971

Dr. Robert A. Kehoe
C/o Mrs. Jeraldine Koughlin
1051 Francisco Street
San Francisco, California 94109

Dear Dr. Kehoe:

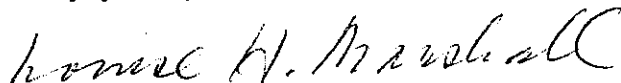
I am writing you at once to let you know how much I appreciate the very great effort you have made to review the draft and to get your material to us.

We had a phone call from your devoted secretary in Cincinnati Monday morning (the 18th), indicating that the longer draft was on its way. It arrived yesterday, the 20th. In the meantime your letter and short draft came by special delivery Monday afternoon, not in time for Dr. Dinman to see it because he had to leave about 3:30.

I have scanned your comments and can say that I believe they are extremely valid. Because of the delay in the postal service, copies of your comments have been sent anonymously, of course, to Dr. Hammond. You were not alone in making the criticisms you did of the first draft. Dr. Hammond is rewriting that entire chapter and I will send you a copy as soon as it becomes available.

Thank you again for your very considerable interest and cooperation. I do hope California is putting out its best weather for you.

Sincerely yours,



Louise H. Marshall, Ph.D.
Professional Associate

LHM/th

N13349.08

KE 0012854

February 22, 1971

Louise H. Marshall, Ph.D.
National Research Council
2101 Constitution Avenue
Washington, D.C. 20418

Dear Doctor Marshall:

It was seemingly impossible for me to complete the critical examination of the Draft Report of the Panel, which you sent to me, without some interruption, which would enable me to attend to some other matters. It was especially necessary for me to prepare a promised paper for the meeting of the American Academy of Occupational Medicine. This has now been done, and the paper was delivered last week in New York. However, when I was in Cincinnati, on February 5 and 6, en route to New York, I delivered to Mrs. Bice, my secretary, the balance of my comments, and obtained from her a copy of my hand-written memorandum to you on certain aspects of Chapter 3 of the Draft which you had sent me. The latter has now been typed and corrected, and sent to Cincinnati for final typing and xeroxing.

Mrs. Bice will forward to you a typed copy of this letter, together with two (2) copies of the other material here referred to. The further comments may be of some further benefit to you and Dr. Dinman, in connection with your final report, and it seems advisable to send them along. If I can be of further assistance, do not hesitate to call on me. I shall return to Cincinnati, to stay, on or about March 2nd. Meanwhile, I continue at editorial work in our temporary residence in San Francisco.

Let me say to you that, despite the critical comments which I have made, the Report in general is, in my view, a creditable piece of work. I am pleased to have had an opportunity to review it, and I believe it will be extremely useful. By contrast with a "Second Draft" of a report on "Criteria, etc." issued in Washington from a source which may well be left unnamed, it is, indeed, a model of good judgment and objectivity. I do not, by this ultra-conservative remark, mean to damn your Report with faint praise, but rather to express my contempt for the other unintelligent document. I find myself amazed at the contribution made by Dr. Chisolm, despite its unduly voluminous and somewhat scattered initial character. I am not quite sure how a matter so varied in nature and so complex in its approaches can be dictated in an intelligible manner. This is something I cannot do. It is not that the result was really good, by my standards of writing, but that it was pretty much all there in intelligible form, and that it can be made very good, indeed, by some judicious rewriting. It is not strictly relevant in all respects, to the question of the hazard of lead absorption at a very low rate, but it indicates, clearly, that the medical appraisal of the onset, course and development of

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Louise H. Marshall, Ph.D.

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February 22, 1971

poisoning due to lead, has been made by physicians (some physicians) with considerable competence. This is an important consideration, in the confused state of mind which has attributed little knowledge of this subject, and little toxicological understanding to physicians generally and specifically.

Cordially yours,

Robert A. Kehoe, M.D.
Professor Emeritus of
Occupational Medicine

RAK:wb

Dictated but not read

KE0012856

Certain Supplementary Interpretations of Physiological Phenomena Concerning the Absorption and Secretion of Lead, Relating to Chapter 3 of the Initial Draft, Entitled

INPUT AND DISPOSITION OF LEAD IN MAMMALIAN SYSTEMS

1. Absorption

a. Skin

The absorption of lead compounds through the skin depends to a considerable extent upon the nature of the compound. So far as the inorganic compounds, alone or in solution in water, are concerned, some degree of penetration through the skin occurs almost certainly, but the extent of the absorption is too slight to be of practical importance. The evidence for this statement, so far as that obtained since analytical methods of great sensitivity and reproducibility have been available, has been hard to obtain since it has been necessary, in most experiments, to find evidence of an appreciable absorption greater than that occasioned in man or animal by his ordinary environmental exposure (intake in food, beverages, and air). This has been easily accomplished in the case of the alkyl lead compounds, which are readily absorbed through the skin, but not so easily with the lead soaps, for example, and not at all in the case of the inorganic salts, excepting through dead animal membranes. As to the latter, the extent of the absorption through the skin of the living animal is quite another matter, which is not revealed by the behavior of dead skin.

Not all of the soaps have been investigated, by any means, but those which are known to have been, have yielded low results. The information on these matters has rarely been published, since brief experiments have yielded little information suitable for publication.

Interestingly enough, while tetraethyllead is absorbed through the skin of animals and man readily, so as to produce acute and fatal illness, tetramethyllead is much less readily absorbed, for quite unknown reasons.

Considered together where the phenomena are more or less inseparable. b. Gastrointestinal Tract
c. Respiratory Tract

(Better Spoken of as Alimentary Tract Since Absorption Occurs in the Mouth and Nasopharynx)

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KE 0012857

The rate of absorption of lead from the alimentary tract varies with the quantity available therein, and, as would be expected, the higher the concentration of lead in the tract, the greater the rate. Under ordinary conditions, (usual quantities available in food and beverages), the absorption may be as little as 5%; when the amounts are increased, the rate is higher, being as much as 12% at 5 or 6 times the usual daily intake of lead. This, however, depends tremendously upon the composition of the alimentary contents. If soluble lead in the tract is precipitated by high concentrations of phosphates, for example, the amount absorbed will be reduced.

Incidentally, it would be impossible, or nearly so, to find out the nature of the compound being absorbed from the highly complex (chemically) contents of the alimentary tract of persons on a varied diet. By determining, precisely, the mixture available for absorption, as for example, following the administration of a solution of a lead salt into an empty alimentary tract (rendered so by taking no food for 48 hours or so), one could be reasonably certain of the nature of the compound being absorbed, but not what it would be shortly thereafter in the complex media of the blood and tissues. The problem of the nature of the compound present in the alimentary tract resolves itself into knowledge of the nature of the compound administered, but the nature of the compounds, which result from chemical reaction in the internal media of the body, is quite another matter.

The quantity of lead absorbed by an individual can be determined approximately by the conduct of a balance experiment over a considerable period of time (months, years), during which everything consumed is measured (in specimens collected in duplicate, quantitatively and qualitatively) for its lead content, and the feces and urine are analysed in their entirety. The amount absorbed is represented by the difference between intake and output over a period of time sufficient, ideally, to neutralize the intrinsic error of the sampling technique. The ordinary "normal," healthy, individual, subsisting on an adequate, but not elaborate, diet (excluding

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exotic foods), and protected against an elevated range of temperature during the hot months of the year, within the temperate area of the country, can serve well as the subject for such an experiment, without any large unmeasured losses of lead from his body in sweat or in alimentary irregularities. The regimen is inconvenient and troublesome, but not unduly demanding of an intelligent, tractable subject employed for the purpose, after his having been completely instructed and warned, so as not to encounter unexpected inconveniences. Moreover, experiments of this type permit, as will no other types (with the possible exception of the use of short-lived radioactive compounds), the discovery of physiological patterns of a descriptive type, into which, without undue assumptions, relatively simple mechanisms can be visualized. For example, subjects to whom lead can be administered within the limits of established safety, can provide satisfactory information concerning many matters related to rates of the absorption and excretion of lead, in relation to dosages of lead administered, and quantities of lead consumed otherwise. Different rates of the excretion of lead, under a variety of ordinary and induced circumstances, provide answers to questions which have long remained unanswered.

Several highly important matters have been elucidated in this manner, instead of resorting to long-lived radiotracers, which cannot be used, beyond very low dosages, for brief periods of time, in dealing with a bone-seeking element, administered to human beings. A few of these facts, which have not been included in the presentation of this Third Chapter, and are not apparent at once without intense study of the elaborate data of such experiments, are indicated, in relation to the alimentary absorption of lead, in the following paragraphs.

1. The normal or regular alimentary absorption of lead by the human organism is a continuous process, e.g., continuing, hour after hour, and day after day, and year after year, at somewhat varying rates, under normal conditions, (as is the absorption of lead by an individual, via the respiratory tract, in living his life in

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a variably lead-containing ambient atmosphere). The reason for this lies, in the former instance, in the length of time involved in the passage of lead-containing food through the alimentary tract, following the intake of meals, and during the intervals between. There is variability in the rate of absorption, no doubt, because of the variability (for a number of reasons) of the concentration of lead in different parts of the alimentary tract from hour to hour and day to day, as, indeed, there is variability, for other reasons, in the rate of the absorption of lead from the respiratory tracts of individuals.

2. The absorption of lead associated with occupational exposure to lead, on the other hand, is grossly variable in rate, and in effect is intermittent in rate, by virtue of the hours of work, generally only 40 out of the 168 hours of the week, provided that the absorption of lead via the respiratory tract during work hours, and for only a short time thereafter, is the only important source of the absorbed lead. That is provided the airborne lead is not diverted, because of the size of the particles inhaled, into the alimentary tract, to be available for absorption, until the alimentary tract has been almost completely evacuated. The latter type of exposure to lead does not limit absorption to the hours of work, but translates the apparently intermittent exposure (and absorption) of lead into a nearly continuous exposure (and absorption), perhaps with serious consequences. Under certain circumstances, the ingestion of lead with food, beverages, tobacco, etc. handled with unclean hands, may be considerable.

3. The significance of these facts lies in the circumstance that continuous absorption of lead (as in the ambient atmosphere, and in the daily ingestion (swallowing) of lead) results in a continuous rate of its accumulation in the body. Intermittent exposure (as in occupational exposure, limited, for all practical purposes, to the hours of work), to the contrary, results in intermittent accumulation, followed by intermittent loss from the body (proportional to the amounts absorbed) at elevated levels, during the hours of no or greatly reduced exposure. This results in an

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eventual equilibrium between intake and output of lead, whereby a level of quantity or concentration in the body is reached, and is not appreciably increased so long as the exposure (dosage) remains constant. This is the sole basis, in principle and performance for providing actually safe conditions of employment for persons who are absorbing lead from the air in quantities, over limited periods of time, which under the conditions of continuous exposure would be grossly dangerous. The duration of exposure, therefore, is just as important, in the strictly quantitative sense of lead absorbed, as is the amount of the dose absorbed during a single period of exposure. This is also the only possible factor of danger involved in very low concentrations of lead in the ambient air, which in variable amounts (dependent upon one's location, his rate of respiration at work, at rest and in sleep, and certain other minor factors) are absorbed in the respiratory tract (and only a small amount in the alimentary tract) during every hour of the day and night of every day of life. The safe concentration of lead in the air, therefore, is that which can be breathed every day of one's life, without inducing a dangerous degree of accumulation in the body of man during his lifetime. It is obvious that there is such a "safe" amount, or we could not have remained alive and well for the years of our lives. What that safe limit is for all ordinary people, collectively, is the issue.

Efforts have been made in experiments making use of normal healthy subjects, to determine the quantity (concentration) of respirable lead, actually measured with care (and reduced to such uniform size of particle as would seem to prevent any significant amount of clearance from the respiratory into the alimentary tract), which can be breathed, continuously, without inducing such a degree of accumulation in the body of man as would result in any measureable increase in the rate of the urinary excretion of lead, or in a measureable increase in the concentration of lead in the blood of the individual subject.

Two primary physiological hypotheses provide the basis for this type of

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experimentation. One rests on the concept that the intermittent respiratory exposure of experimental subjects, (since they cannot be subjected to continuous exposure without very elaborate facilities for continuous living, daily, over some considerable period of time, in a known atmosphere containing a known quantity of lead), can be converted by calculation (extrapolation) into continuous exposure, by subjecting persons to a known concentration of lead in air for graduated fractional parts of the time, each fractional period being continued for the time (weeks, months) required to reach the type of equilibrium described above. A sloping line is drawn (a straight line appears to be entirely satisfactory) through the several levels of the equilibrated concentration of lead in the urine or blood (or both) arrived at during the respective periods of observations, so as to locate the concentration associated with exposure all day every day. For example, a certain level in blood or urine is reached (perhaps the starting level undergoes no elevation) at the end of four months of exposure at 20 hours per week; a higher level is reached (if the exposure is not insufficient to induce a change) at the end of 40 hours per week; and successively, a different point of concentration is reached at the end of 80 and 120 hours per week, respectively. A line is projected through these points and on to 168 hours per week, involving continuous exposure. If there is a statistically significant elevation of the absorption of lead at any time during these observations, as revealed by the quantities of lead in the blood or urine, the experimentally induced concentration of lead in the air is probably too high for human safety, since a measureable increase in the concentration of lead in the urine or blood signifies a detectable absorption and retention of lead in the body.

The second hypothesis referred to above has to do with the interpretation of the results obtained by such experimentation as that described above, on the basis of animal experimentation (during which some of a group of animals can be destroyed for analysis of their tissues at any appropriate time). It seems evident that some

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degree (perhaps only a very slight degree), of accumulation of lead occurs, whenever the urine and blood give indication of this through any demonstrable change. (Such change is due to the concentration of lead in the air, if the intake of lead in food and beverages can be kept very nearly constant, so that one can be sure that the change has not been occasioned by temporary gross variations, upward, of absorption from the alimentary tract. It has been found to be difficult to achieve an adequate control of this variable, when subjects have given free reign to their choices, in the matter of their dietary composition. This is the greatest experimental difficulty in this type of experimentation.) The extent of the change observed bears a close relationship to the degree of accumulation in the body. There is also evidence that, when the rate of accumulation is low, the lead so accumulated is to be found mainly in the dense bone of the skeleton (into which it moves slowly from the trabecular and more vascular bone, and from which it cannot escape, either through normal metabolic mechanisms, nor through the administration of chelating agents, except at the very slow rate of the metabolism of dense bone). Thus far, no means, short of the disintegration of the dense bones, as in osteoporosis, has been observed to be effective in increasing the rate of the loss of lead from such dense bones. It is, for all practical purposes, entrapped lead, which enters only at a very low rate, regardless of its quantity, into the metabolic activities of the organs and soft tissues of the body.

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