LI-94

HARVARD UNIVERSITY
OFFICE OF THE EXECUTIVE SECRETARY

COMMITTEE ON RESEARCH AND DEVELOPMENT
[illegible] BRATTLE STREET · BOSTON, MASSACHUSETTS [illegible]

July 20, 1967

AUG 3 1967

Don G. Fowler, Project Manager
International Lead Zinc Research Organization
292 Madison Avenue
New York, New York 20017

Dear Mr. Fowler:

I am enclosing herewith an application for continued support of the project entitled, "Study on Biological Basis of Lead Intoxication" under the direction of Dr. Bert L. Vallee, Professor of Biological Chemistry at the Harvard Medical School.

This request is for a one-year period beginning January 1, 1968, in the amount of $52,655.40.

This application has the approval of Dr. Elkan R. Blout, Head of the Department of Biological Chemistry of the Harvard Medical School and of Dr. Robert H. Ebert, Dean of the Harvard Medical School.

If there is any further information you desire, please do call on me.

Sincerely yours,

Henry C. Meadow
Executive Secretary

HCM/cj

Encs.

LIA12358

PROPOSED BUDGET FOR STUDY ON BIOLOGICAL BASIS OF LEAD INTOXICATION

Personnel	
Research Associate, full time	$14,000.00
Retirement, social security, etc.	
Harvard Composite Rate, 16%	2,240.00
Two technicians, full time	12,200.00
Harvard Composite Rate, 9 3/4%	1,189.50
Chemicals and Glassware	4,000.00
Animals	
Includes purchase and maintenance, special diets, plastic cages, etc.	7,800.00
Shop Time	
Includes construction of lighted culture racks for growth of microorganisms	[illegible]
Travel	
Includes traveling to animal center (51 miles)	[illegible]
Publications	
Includes journal costs and reprints, graphs for publication, typing of Annual Progress Report	[illegible]
Total	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]

N 543.01

ILZRO PROJECT SUMMARY

Issue Date: August 1967

PROJECT NO. LE-94 TITLE Study of the Biological Basis for Lead Intoxication

PREVIOUS IDENTIFICATION ULC-16 Study of the Biological Basis for Lead Intoxication

CONTRACTOR Harvard Medical School

CURRENT CONTRACT January 1, 1967 to December 31, 1967. $34,285.20

CUMULATIVE EXPENSES (to July 31, 1967) $77,183.00

1968 PROPOSED OR CONTRACT PRICE $52,853.40

1968 AUTHORIZATION

1967 & Prior Authorizations Uncommitted	none
1968 Proposed Authorization	$52,853.40
Undesignated Research Authorization	none
1968 Proposed or Contract Price	$52,853.40

MARKET APPLICATIONS To all lead markets and uses.

OBJECTIVE To provide fundamental understanding of the toxic mode of action of lead in biological materials and to further the understanding of the metabolism of lead and mechanisms of heavy metal detoxification in general.

RESEARCH REVIEW

1. Current Status The isolation of metallothionein from rabbit kidneys has been achieved and it has been demonstrated that lead is associated with this protein when it is purified from the kidneys of lead-intoxicated rabbits. A lead intoxication study is also being carried out using a pony. Detailed experimental conditions for inhibition of the microorganism, Rhodopseudomonas spheroides, by lead acetate have been established. A specific lesion in tetrapyrrole metabolism through which manganese and lead interfere with synthesis of both heme and bacteriochlorophyll has been identified. This establishes that lead toxicity can operate through the well-known mechanism of metal ion antagonism. Current studies now range from investigations intended to improve the analytical chemistry of lead, through interactions of lead with enzymatic and nonenzymatic proteins, to effects of lead upon the metabolism of microorganisms, and finally to investigation of the intoxication of lead in higher species including mammals.

2. Projected Research Attempt to isolate liver ribonucleic acid, which has been shown to contain metals such as chromium, manganese and nickel, and determine if lead interacts with this material. Attempt to determine if lead displaces zinc from liver alcohol dehydrogenase, a possibility suggested by the in vitro experiments.

3. Reports Issued
   a. Progress Reports - from 1/1/65 to 7/20/67, three. Last report covered the period 8/1/66 to 7/1/67.
   b. Proposal - PROPOSED BUDGET FOR STUDY ON BIOLOGICAL BASIS OF LEAD INTOXICATION (received August 4, 1967).
   c. Work Statement - none

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DEVELOPMENT REVIEW

1. Pilot Production - not applicable
2. Consumer Evaluation - not applicable
3. Licensing Activities - not applicable
4. Patents - not applicable
5. Publications
   a. ILZRO - none
   b. Development Associations - none

ECONOMIC INCENTIVE

1. Market Goals - Defense of markets such as TEL, paint, can solder, presently assailed by allegations of toxic reaction. Expand lead use into areas, such as auto body painting, where allegations of toxic hazards mitigate against use.

2. Applications and Market Volume - All lead uses.

3. Size of Market Defending - Application to all lead markets.

4. Competitive Threat - Defensive against competition and legal restrictions.

advantage not only of larger kidneys but also of [illegible] large amounts of other tissues which will be [illegible] for several types of studies planned for the coming year. We are currently isolating metallothionein from the kidneys of the lead-poisoned animals and will next attempt a [illegible] isolation of metallothionein from liver tissue. [illegible] in the report, we also hope to isolate liver ribonucleic acid, which we have shown to contain metals [illegible] manganese and nickel, and to determine if lead binds to [illegible] this material. Similarly, we will attempt to determine if [illegible] zinc from liver alcohol dehydrogenase, [illegible] in vitro [illegible] we are increasingly turning to animal [illegible] the significance of [illegible] larger animals such as [illegible]

[illegible]

Mr. Don [illegible] Fowler July 20, 1967

The gross effect of lead on porphyrin metabolism in man and other higher forms of life is well-known, manifesting either in anemia or as an abnormal excretion of porphyrins or their precursors. However, the specific sites of action for lead have not been clearly delineated in vivo. The studies with Rhodopseudomonas presage both the localization of the defect and the variables that may affect it and, perhaps, be employed diagnostically. It is rewarding that the metabolism of a microorganism seems to serve as a suitable test system, bearing out our anticipations.

Previous Progress Reports have described several of our in vitro investigations of potential interactions of lead with crucial enzymatic systems. These efforts were stated to be exploratory since it was our intention to delineate biological systems which might be sensitive to lead in vitro as a prelude to investigating possible in vivo counterparts, which might predict the chemical nature of the site of action. Recently, we have found a very good example of such a system, lipoamide dehydrogenase. Our [illegible] tests indicate that lead interacts very strongly with this enzyme, presumably through sulfhydryl linkages at the active enzymatic site. Examination of the influence of coenzymes and substrates on the lead inhibition, and its reversal by EDTA, indicate that this should be a most interesting and important enzyme for further study. We intend to explore this more thoroughly in microorganisms and higher forms during the coming months.

It may be of interest to point out that our current studies of the biological basis for lead intoxication now range from investigations intended to improve the analytical chemistry of lead, through interactions of lead with enzymatic and nonenzymatic proteins, to effects of lead upon the metabolism of microorganisms, and finally to investigation of the interaction of lead in higher species including man. During the past two years we have gained experience with effects of lead in each of these areas; the diversity of this approach now allows us to select for each experiment a system of biological complexity which is most suitable for the purpose at hand. The breadth of operations available to us in these and related areas should prove increasingly advantageous as this work continues.

Lastly, the work is now at a stage where it would appear