LEAD INDUSTRIES ASSOCIATION, INC.
292 MADISON AVENUE
NEW YORK 17, N. Y.

October 24, 1962

To Members of the Health and Safety Committee:

Attached is background information received from Dr. Dorfman at the Worcester Research Foundation covering item No. 4 on our proposed agenda for the November 13 Health and Safety Committee Meeting.

Please be prepared to discuss this as a possible industry-sponsored project.

Very truly yours,

Don O. Fowler
Secretary

DOF:md
cc: Dr. Y. E. Lebedeff
Enc.

Lead Ahead with Lead

THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY

Shrewsbury, Massachusetts

October 22, 1962

RESEARCH REQUEST

To: Lead Industry Committee
292 Madison Avenue
New York 17, New York

Title of Research: THE TESTING OF ORGANOLEAD COMPOUNDS FOR POSSIBLE ENDOCRINOLOGICAL AND ANTI-MAMMARY TUMOR ACTIVITY.

General Statement: Dr. Malcolm C. Henry of Natick, Massachusetts, has given and intends to continue to give us various organolead compounds for testing. In the past we have already found some compounds with possible important utilities. We wish to continue these studies. Our tests will include androgenic activity (male sex hormone), estrogenic activity (female sex hormone), anti-estrogenic (possible anti-tumor activity), anti-androgenic activity (possible treatment of prostatic cancer), and anti-inflammatory activity (possible treatment for rheumatoid arthritis and allergic diseases).

We should also be pleased to study organolead compounds from other sources.

Budget: December 1, 1962 to November 30, 1963

1 Bioassay Technician	$ 5,000
Rats, Mice and Chicks	3,000
Consumable Supplies	1,000
Direct Costs	$ 9,000
Indirect Costs 25%	2,250
TOTAL	$11,250

Signed:
Ralph I. Dorfman

RID/g

THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY

Shrewsbury, Massachusetts

PROGRESS REPORT
TO THE LEAD RESEARCH COMMITTEE
January 1 to August 31, 1962

Enclosed are 10 tables which summarize our activities with organolead compounds over the past eight months. Some twenty-two compounds were supplied to us by Dr. Malcolm Henry during this period. These compounds are listed by code number and name. The Tables 2 through 8 list the results.

No activity was detected when the compounds were tested as possible female sex hormones (Tables 2 and 3). Table 4 presents the results of compounds HP-1, HP-7 and HP-15 which showed statistically significant anti-androgenic activity on the chick's comb. Compound HP-15 was active as an anti-androgen in the rat but some toxicity was observed. Anti-androgenic activity in the rat was also observed at the 2 mg level (Table 7). Compounds with this type of activity could be valuable therapeutic agents in prostatic cancer, masculinized women due to ovarian or adrenal cancer, and could possibly be of importance in acne, baldness, and as compounds to inhibit beard growth in men.

In Table 9 HP-13 and HP-14 may have some anti-inflammatory activity. Compounds with this type of pharmacological activity are usually valuable in rheumatoid arthritis, allergies, and asthma.

Respectfully submitted,

Signed:

Ralph I. Dorfman

RID/g
Enc.

Table 1

ORGANOLEAD COMPOUNDS

Code	Name
KP 1	Tetraphenyllead
KP 2	Triphenyllead Chloride
KP 3	Triphenyllead Iodide
KP 4	Diphenyllead Dichloride
KP 5	Diphenyllead Diacetate
KP 6	Hexaphenyldilead
KP 7	Bis-triphenyllead sulphide
KP 8	Triphenylmethyllead
KP 9	Triphenylthiomethyllead
KP 10	Diphenylchlorolead Acetate
KP 11	Thioethyltriphenyllead
KP 12	Thiopropyltriphenyllead
KP 13	Thiobenzyltriphenyllead
KP 14	Thiophenyltriphenyllead
KP 15	Thioacetyltriphenyllead
KP 16	Thiobenzoyltriphenyllead
KP 17	Lead Methyl Mercaptide
KP 18	Lead Ethyl Mercaptide
KP 19	Lead 1-propyl Mercaptide
KP 20	Lead 1-butyl Mercaptide
KP 21	Lead Benzyl Mercaptide
KP 22	Lead Thiophenolate

Table 2

THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY
Shrewsbury, Massachusetts

ASSAY REPORT

Estrogen Assay
(Subcutaneous Injection)

Submitted by: Dr. Henry
Samples Tested: As Listed
Test Animal: Mouse, female, 19-21-day-old
Vehicle: Sesame oil, 0.1 ml. per injection
Procedure: Injected once daily for 3 consecutive days and autopsy on 4th day.

Material Administered	Total Dose µg.	No. of Mice	Mean Uterine Ratio ± S.E.
0	0	8	0.80 ± 0.017
Estrone	0.05	8	1.05 ± 0.109
	0.4	8	4.61 ± 0.186
HP 1	1 mg.	5	0.83 ± 0.068
HP 2	1 mg.	6	0.76 ± 0.029
HP 3	1 mg.	4	0.88 ± 0.118
HP 5	1 mg.	6	3.91 ± 0.105
HP 6	1 mg.	6	0.71 ± 0.041
HP 7	1 mg.	6	0.87 ± 0.092
HP 8	1 mg.	6	0.78 ± 0.052
HP 9	1 mg.	ALL DEAD	
HP 11	1 mg.	2	1.03 ± 0.187
HP 12	1 mg.	6	1.03 ± 0.100
HP 13	1 mg.	6	0.77 ± 0.056
HP 14	1 mg.	6	0.68 ± 0.041
HP 15	1 mg.	ALL DEAD	
HP 16	1 mg.	3	0.85 ± 0.085
HP 17	1 mg.	6	0.81 ± 0.057
HP 18	1 mg.	6	0.84 ± 0.063
HP 20	1 mg.	4	1.02 ± 0.079
HP 21	1 mg.	6	0.85 ± 0.037
HP 22	1 mg.	6	1.03 ± 0.111
HP 4	1 mg.	5	0.92 ± 0.067

N 330.04

Table 3

Worcester Foundation For Experimental Biology
Shrewsbury, Massachusetts

ASSAY REPORT

Estrogen Assay
(Subcutaneous Injection)

Submitted by:
Samples Tested:
Test Animal: Mouse, female, 19-21-day old
Vehicle: Sesame oil, 0.1 ml. per injection
Procedure: Injected once daily for 3 consecutive days and autopsy on 4th day.

Material Administered	Total Dose ug.	No. of Mice	Mean Uterine Ratio ± S.E.
0	0	10	0.97 ± 0.045
Estrone	0.05	10	1.84 ± 0.223
	0.1	10	1.53 ± 0.121
	0.2	9	3.94 ± 0.325
	0.4	10	4.53 ± 0.193
EP-15	100	6	0.66 ± 0.068
E-20	1	10	0.85 ± 0.076
	10	10	1.01 ± 0.045
	100	10	0.83 ± 0.055
E-21	1	10	0.84 ± 0.053
	10	10	1.15 ± 0.096
	100	10	0.64 ± 0.028

N 330.05

Worcester Foundation for Experimental Biology
Shrewsbury, Massachusetts

Table 4

ASSAY REPORT

Chick Anti-Androgen Assay

Submitted by: Dr. Henry
Samples Tested: As Listed
Test Animal: Day-old male white Leghorn Chick.
Vehicle: Testosterone enanthate, sesame oil, 0.5 ml. Test material, sesame oil, 0.05 ml. per injection.
Procedure: On first day chicks are injected once with testosterone enanthate. Beginning on same day inject test material once daily for 7 days and autopsy on 8th day.

TEST MATERIAL Designation	Total Dose mg.	Testosterone Enanthate Total Dose mg.	No. of Chicks	Mean Body Wt. g.	Mean Comb Ratio ± S. E.
0	0	0	11	53	0.28 ± 0.019
0	0	0.5	12	61	0.98 ± 0.043
RO-27239	0.25	0.5	10	54	0.77 ± 0.066
RO-27239	1.0	0.5	10	62	0.66 ± 0.041
HP-1	1	0.5	10	57	0.86 ± 0.065
HP-2	1	0.5	10	61	0.96 ± 0.046
HP-3	1	0.5	9	63	0.99 ± 0.048
HP-7	1	0.5	10	56	0.86 ± 0.084
HP-6	1	0.5	10	59	1.06 ± 0.076
HP-5	1	0.5	9	60	0.92 ± 0.105
HP-8	1	0.5	10	63	1.02 ± 0.079
HP-9	1	0.5	9	59	1.19 ± 0.066
HP-11	1	0.5	9	55	1.21 ± 0.089
HP-12	1	0.5	10	55	1.13 ± 0.104
HP-13	1	0.5	10	54	1.13 ± 0.121
HP-14	1	0.5	10	57	0.96 ± 0.092
HP-15	1	0.5	9	57	0.81 ± 0.065
HP-16	1	0.5	10	55	1.28 ± 0.081
HP-17	1	0.5	10	57	0.93 ± 0.096
HP-18	1	0.5	10	54	1.02 ± 0.097
HP-19	1	0.5	10	62	0.99 ± 0.060
HP-20	1	0.5	10	53	0.96 ± 0.071
HP-21	1	0.5	10	56	1.05 ± 0.082
HP-22	1	0.5	10	56	0.93 ± 0.098
HP-4	1	0.5	9	59	1.07 ± 0.115

N 330.06

Worcester Foundation for Experimental Biology
Shrewsbury, Massachusetts

TABLE 5
ASSAY REPORT

Chick Anti-Androgen Assay

Submitted by: Dr. Malcolm C. Henry
Samples Tested: E-15
Test Animal: Day-old male white Leghorn Chick.
Vehicle: Testosterone enanthate, sesame oil, 0.1 ml. Test material, sesame oil, 0.05 ml. per injection.

Procedure: On first day chicks are injected once with testosterone enanthate. Beginning on same day inject test material once daily for 7 days and autopsy on 8th day.

TEST MATERIAL Designation	Total Dose mg.	Testosterone Enanthate Total Dose mg.	No. of Chicks	Mean Body Wt. g.	Mean Comb Ratio ± S. E.
0	0	0	12	58	0.68 ± 0.047
0	0	0.5	9	60	1.23 ± 0.095
Ro 2-7239	1	0.5	9	57	0.86 ± 0.054
	0.5	0.5	9	60	1.05 ± 0.054
MP 15	3	0.5	10	57	1.83 ± 0.108

N 330.07

Table 6

Worcester Foundation for Experimental Biology
Shrewsbury, Massachusetts

ASSAY REPORT

Rat Anti-Androgen Assay
(Injection)

Submitted by:
Samples Tested:
Test Animal: Rat, male, 21-day-old.
Vehicle: Testosterone, CMC, 0.5 ml. per injection
Test material, CMC, 0.5 ml. per injection
Procedure: Castrate 21st - 28th day of life. Beginning on same day, administer treatments at separate sites once daily for 7 days and autopsy on 8th day.

TEST MATERIAL Designation	Total Dose mg.	Testosterone Total Dose mg.	No. of rats	Mean Body Wt. g.	TISSUE RATIO ± S. E. Prostate	Seminal Vesicles	Levator Ani
0	0	0	7	78	0.16±0.019	0.10±0.001	0.24±0.032
Testosterone	0	2	10	82	1.30±0.108	1.12±0.077	0.74±0.033
Progesterone	125	2	10	88	1.07±0.058	0.72±0.045	0.58±0.027
	250	2	10	83	1.10±0.066	0.70±0.056	0.54±0.024
RP-15	30	2	0**				

** 5 DEAD

N 330.08

Table 7

Worcester Foundation for Experimental Biology
Shrewsbury, Massachusetts

ASSAY REPORT

Rat Anti-Androgen Assay
(Injection)

Submitted by: Dr. Malcolm Henry
Samples Tested: KP-15
Test Animal: Rat, male, 21-day-old.
Vehicle: Testosterone, CMC, 0.5 ml. per injection
Test material, CMC, 0.5 ml. per injection
Procedure: Castrate 21st - 28th day of life. Beginning on same day, administer treatments at separate sites once daily for 7 days and autopsy on 8th day.

TEST MATERIAL Designation	Total Dose mg.	Testosterone Total Dose mg.	No. of Rats	Mean Body Wt. g.	TISSUE RATIO ± S. E. Prostate	Seminal Vesicles	Levator Ani
0	0	0	10	86	0.14±0.011	0.10±0.013	0.25±0.018
0	0	2.0	10	84	1.13±0.076	0.67±0.044	0.57±0.010
KP-15	2	2.0	8	76	1.01±0.063	0.53±0.066	0.53±0.037
KP-15*	10	2.0	7	64	0.94±0.071	0.45±0.032	0.35±0.044
KP-15**	20	2.0	ALL DEAD				
KP-15***	50	2	ALL DEAD				

* Rats very sick
** All dead on 5th day
*** All dead on 2nd day

Table 8

The Thymolytic and Anti-Inflammatory

Activity of MIA, B, and C, KP-1, 2, 3, and 4

in the Adrenalectomized Rat

Material Administered	Total Dose mg.	THYMUS TEST No. of Rats	Mean Thymus Ratio ± S.E.	ANTI-INFLAMMATORY TEST No. of Obs.	Mean Dry Tissue Wt. mg. ± S.E.
0	0	7	4.33 ± 0.8185	7	33.2 ± 1.677
Cortisol	0.5	9	3.72 ± 0.3742	9	33.6 ± 2.357
	4.5	10	1.21 ± 0.129	10	16.4 ± 1.531
KP-1	8	3	4.12 ± 0.328	3	27.7 ± 1.767
KP-2	8	ALL DEAD			
KP-3	8	ALL DEAD			
KP-4	8	ALL DEAD			

Table 9

THE THYMOLYTIC AND ANTI-INFLAMMATORY

ACTIVITY OF HP 5, 6, 7, 8, 9, 11, 12, 13 & 14

IN THE ADRENALECTOMIZED RAT

Material Administered	Total Dose mg.	THYMUS TEST No. of Rats	THYMUS TEST Mean Thymus Ratio ± S.E.	ANTI-INFLAMMATORY TEST No. of Obs.	ANTI-INFLAMMATORY TEST Mean Dry Tissue Wt. mg. ± S. E.
0	0	10	3.86 ± 0.308	10	28.4 ± 2.615
Cortisol	4.5	9	2.24 ± 0.194	9	24.9 ± 1.633
HP 5	8	7	3.65 ± 0.204	7	20.6 ± 1.989
HP 6	8	5	3.97 ± 0.198	5	27.1 ± 3.803
HP 7	8	7	4.56 ± 0.269	7	27.0 ± 1.956
HP 8	8	6	4.56 ± 0.377	6	25.1 ± 1.614
HP 9	8	2	2.86 ± 2.050	2	29.1 ± 3.712
HP 11	8	ALL DEAD			
HP 12	8	ALL DEAD			
HP 13	8	3	5.06 ± 0.322	3	17.5 ± 1.840
HP 14	8	4	4.40 ± 0.283	4	16.9 ± 1.360
Cortisol	0.5	6	3.76 ± 0.221	6	24.1 ± 1.816

5, 6, 7, 10, 11 compounds collected under skin.

Table 10

THE THYMOLYTIC AND ANTI-INFLAMMATORY ACTIVITY OF
KP-15, 16, 17, 18, 19, 20, 21, 22

IN THE ADRENALECTOMIZED RAT

Material Administered	Total Dose mg.	THYMUS TEST No. of Rats	Mean Thymus Ratio ± S.E.	ANTI-INFLAMMATORY TEST No. of Obs.	Mean Dry Tissue Wt. g. ± S. E.
0	0	5	4.20 ± 0.261	5	29.5 ± 3.402
Cortisol	0.5	8	3.81 ± 0.386	8	27.0 ± 2.551
	4.5	10	1.94 ± 0.156	10	17.0 ± 1.083
KP-15	8	1	5.15	1	16.2
KP-16	8	1	3.32	1	22.6
KP-17	8	5	4.29 ± 0.241	5	23.0 ± 1.928
KP-18	8	8	4.37 ± 0.220	8	23.6 ± 1.557
KP-19	8	7	4.17 ± 0.260	7	27.2 ± 2.308
KP-20	8	8	4.26 ± 0.129	8	25.7 ± 2.766
KP-21	8	4	4.04 ± 0.187	4	26.8 ± 1.931
KP-22	8	6	4.32 ± 0.273	6	21.0 ± 1.217