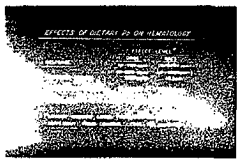
N36832

PATENT PENDING

INSERT FILM EMULSION SIDE DOWN

DATE _____ ASSIGNMENT _____ FILE NO. _____

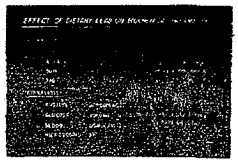


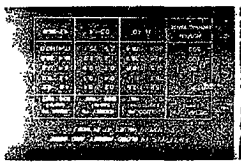


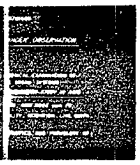


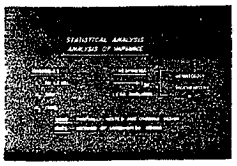


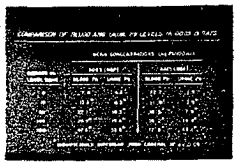


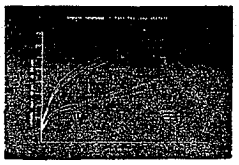


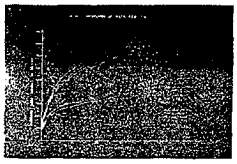




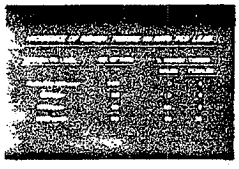


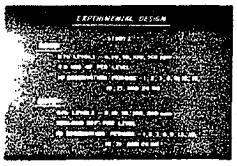




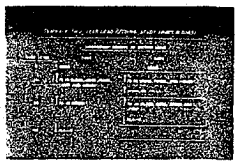


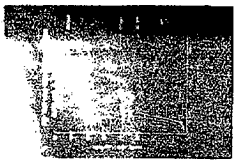


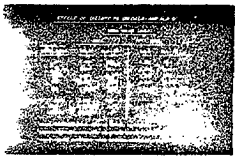


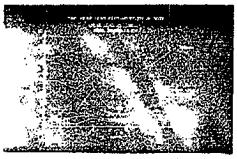


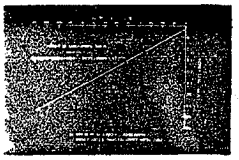


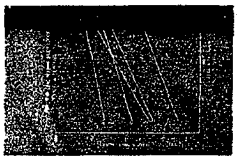


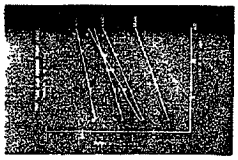


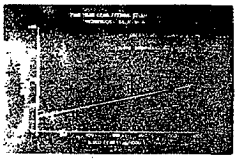


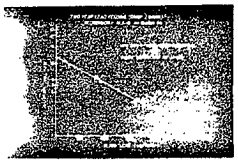




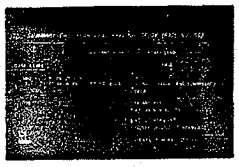


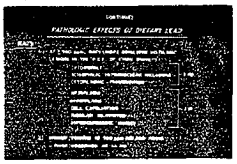


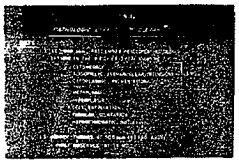


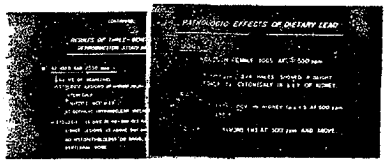


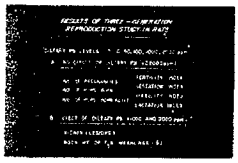


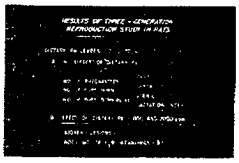












PRINT FILE, NEGATIVE PRESERVER

PRINT FILE BOX 100 SCHENECTADY, N.Y. 12304

DUP050308434

RESULTS OF THREE – GENERATION REPRODUCTION STUDY IN RATS

DIETARY Pb LEVELS – 0, 10, 50, 100
1000, 2000 ppm

A. UP TO 100 ppm, NO EFFECT OF DIETARY Pb ON :

NO. OF PREGNANCIES	FERTILITY INDEX
NO. OF PUPS BORN	GESTATION INDEX
NO. OF PUPS BORN ALIVE	VIABILITY INDEX
AV. WT. OF WEANLINGS	LACTATION INDEX

– HISTOLOGY OF 21-DAY WEANLINGS (F_3B)

DUP050308435

PATHOLOGIC EFFECTS OF DIETARY LEAD

DOGS :

1.) NONE IN FEMALE DOGS UP TO 500 ppm.

2.) AT 500 ppm, 2/4 MALES SHOWED A SLIGHT DEGREE OF CYTOMEGALY IN P.C.T.

DUP05030843

RESULTS OF THREE – GENERATION REPRODUCTION STUDY IN RATS

DIETARY Pb LEVELS – 0, 10, 50, 100, 1000, 2000 ppm

A. NO EFFECT OF DIETARY Pb (≤2000ppm):

NO. OF PREGNANCIES	FERTILITY INDEX
NO. OF PUPS BORN	GESTATION INDEX
NO. OF PUPS BORN ALIVE	VIABILITY INDEX
	LACTATION INDEX

B. EFFECT OF DIETARY Pb (1000 AND 2000 ppm):

KIDNEY (LESIONS)

BODY WT. OF F_3B WEANLINGS (↓)

DUP050308437

INCIDENCE OF KIDNEY TUMORS IN RATS FED LEAD

DIETARY Pb LEVEL	NO. OF RATS	% KIDNEY TUMORS	
		MALES	FEMALES
0, 10, 50, 100 ppm	500	0	0
500 ppm	100	10	0
1000 ppm	40	50	0
2000 ppm	40	80	35

DUP050308438

PATHOLOGIC EFFECTS OF DIETARY LEAD

DOGS :

1.) NONE IN FEMALE DOGS AT $\leq$ 500 ppm .

2.) AT 500 ppm , 2/4 MALES SHOWED A SLIGHT DEGREE OF CYTOMEGALY IN p.c.t. OF KIDNEY.

RATS :

1.) HISTOPATHOLOGY IN KIDNEY (p.c.t.) AT 500 ppm AND ABOVE .

2.) KIDNEY TUMORS (M) AT 500 ppm AND ABOVE.

DUP050308439

EFFECTS OF DIETARY Pb ON HEMATOLOGY

RESPONSE	EFFECT LEVEL*	
	DOGS (0-500 ppm)	RATS (0-2000 ppm)
STIPPLED CELLS	500 ppm	10 ppm
HEMATOCRIT	NONE	1000 ppm
HEMOGLOBIN	NONE	1000 ppm

*LOWEST DIETARY LEVEL THAT WAS SIGNIFICANTLY DIFFERENT FROM CONTROL LEVEL AT $p < 0.05$.

DUP050308440

EFFECT OF DIETARY LEAD ON CLINICAL OBSERVATIONS

	DOGS (0 – 500 ppm)	RATS (0 – 2000 ppm)
APPEARANCE	N	N
BEHAVIOR	N	N
NEUROLOGICAL EXAM	N	–
GROWTH	N	↓ AT ≥ 1000 ppm
MORTALITY	N	↑ IN MALES AT 500 ppm AND ABOVE

N = NO EFFECT

– = NOT PERFORMED

DUP050308441

CONTINUED

PARAMETERS UNDER OBSERVATION

V. PATHOLOGY

- GROSS AND HISTOLOGICAL EXAMINATION OF TISSUES FROM ALL ORGAN SYSTEMS

VI. THREE-GENERATION REPRODUCTION STUDY IN RATS

- 0, 10, 50, 100, 1000, AND 2000 ppm Pb
- INDICES OF FERTILITY, GESTATION, LIVE BIRTH, AND LACTATION
- GROWTH CHARACTERISTICS AND PATHOLOGY OF WEANLINGS

DUP050308442

EXPERIMENTAL DESIGN

STUDY I

DOGS:

5 Pb LEVELS – 0, 10, 50, 100, 500 ppm

4 M AND 4F PER LEVEL

10 OBSERVATION PERIODS – 1, 2, 3, 6, 9, 12, 15, 18, 21, AND 24 MO.

RATS:

5 Pb LEVELS – 0, 10, 50, 100, 500 ppm

50 M AND 50 F PER LEVEL

10 OBSERVATION PERIODS – 1, 2, 3, 6, 9, 12, 15, 18, 21, AND 24 MO.

DUP05030844 3

CONTINUED

EXPERIMENTAL DESIGN

STUDY III

RATS:

3 Pb LEVELS – 0, 1000, 2000 ppm

20 M AND 20 F PER LEVEL

6 OBSERVATION PERIODS – 1, 2, 3, 12, 18, AND 24 MO.

DUP050308444

PARAMETERS UNDER OBSERVATION

I. CLINICAL OBSERVATIONS

- APPEARANCE AND BEHAVIOR
- NEUROLOGICAL EXAM (DOGS)
- GROWTH AND MORTALITY

II. LEAD ANALYSES

- BLOOD, URINE, AND FECES
- TISSUES (BONE, LIVER, KIDNEY, BRAIN, ETC.)

DUP050308445

CONTINUED

PARAMETERS UNDER OBSERVATION

III. HEMATOLOGY

- COMPLETE BLOOD COUNT
- Hct., Hb., AND STIPPLED CELLS
- PROTHROMBIN TIME

IV. BIOCHEMISTRY

- LIVER FUNCTION (A–PASE, GPT, A/G, BUN)
- URINALYSIS (VOL., OSMOL., pH, PROT., MICROSCOPIC)
- SPECIAL TESTS (DALA, ALA–D)

DUP05030844 6

CONTINUED

RESULTS OF THREE-GENERATION REPRODUCTION STUDY IN RATS

B. AT 1000 AND 2000 ppm

↓ AV. WT. OF WEANLINGS

HISTOLOGIC LESIONS OF KIDNEY IN 21-DAY WEANLINGS

- CYTOMEGALY
- ↑ MITOTIC ACTIVITY
- ACIDOPHILIC INTRANUCLEAR INCLUSIONS

HISTOLOGIC LESIONS IN 40-DAY OLD RATS (F_3A AND

- KIDNEY LESIONS AS ABOVE BUT MORE SEVERE
- NO HISTOPATHOLOLOGY ON BRAIN, SPINAL CORD, C VERTEBRAL BONE

DUP050308447

CONTINUED

PATHOLOGIC EFFECTS OF DIETARY LEAD

RATS:

1.) AT ≥ 500 ppm, RATS (M&F) DEVELOPED HISTOLOGIC LESIONS IN THE P.C.T. OF THEIR KIDNEYS:

- CYTOMEGALY
- ACIDOPHILIC INTRANUCLEAR INCLUSIONS
- CYTOPLASMIC PIGMENTATION

— 3 MO.

- METAPLASIA
- HYPERPLASIA
- CELL EXFOLIATION
- TUBULAR DILATATION
- HYPERCHROMATIC NUCLEI

— 1 YR.

2.) KIDNEY TUMORS AT 500 ppm (M) AND ABOVE
- FIRST OBSERVED AT 14 MO.

DUP050308448

EFFECT OF DIETARY Pb ON DALA AND ALA-D

DIETARY Pb LEVEL (ppm)	MEAN VALUES (M&F) RATS DALA[1]	RATS ALA-D[2]	DOGS DALA	DOGS ALA-D
0	0.418	22.0	0.257	23.4
10	0.434	22.2	0.273	21.8
50	0.425	14.4*	0.290	17.8
100	0.437	9.3*	0.268	10.6*
500	0.968*	3.6*	0.574*	3.9*
0	0.492	17.3		
1000	2.091*	2.4*		
2000	2.377*	1.6*		

[1] DELTA-AMINOLEVULINIC ACID IN URINE, mg/100 cc.

[2] DELTA-AMINOLEVULINIC ACID DEHYDRASE ACTIVITY IN BLOOD, UNITS/ml rbc.

*SIGNIFICANTLY DIFFERENT FROM CONTROL LEVEL AT $p<0.05$.

DUP050308449

EFFECT OF DIETARY LEAD ON BIOCHEMICAL PARAMETERS

LIVER FUNCTION :

SGPT

A-PASE

BUN

A/G

NO DIETARY LEAD EFFECT IN RATS OR DOGS

URINALYSIS :

PROTEIN	APPEARANCE
GLUCOSE	VOLUME
BLOOD	OSMOLARITY
MICROSCOPIC	pH

NO DIETARY LEAD EFFECT IN RATS OR DOGS

DUP050308450

RAT MORTALITY FROM DIETARY LEAD

Pb LEVEL (ppm)	NO. OF RATS PER LEVEL	PERCENT MORTALITY *	
		MALES	FEMALES
0	100	37	34
10	50	36	30
50	50	36	28
100	50	36	28
500	50	52	36
0	20	50	35
1000	20	50	50
2000	20	80	35

* INCLUDES RATS FOUND DEAD OR SACRIFICED IN EXTREMIS.

DUP05030845 1

COMPARISON OF BLOOD AND URINE Pb LEVELS IN DOGS & RATS

DIETARY Pb LEVEL (ppm)	MEAN CONCENTRATIONS (µg Pb/100ml)			
	DOGS (M&F)		RATS (M&F)	
	BLOOD Pb	URINE Pb	BLOOD Pb	URINE Pb
0	7.8	4.2	12.7	1.9
10	13.3*	6.2*	11.0	3.9*
50	22.1*	10.3*	18.5*	7.9*
100	28.9*	15.6*	35.2*	14.8*
500	47.2*	32.5*	77.8*	45.1*

* SIGNIFICANTLY DIFFERENT FROM CONTROL AT $p < 0.05$

DUP05030845 2

STATISTICAL ANALYSIS
ANALYSIS OF VARIANCE

VARIABLES	RESPONSES
X_1 Pb LEVEL	$Y_1 \longrightarrow Y_{37}$
X_2 SEX	– LEAD ANALYSES
X_3 TIME	

- HEMATOLOGY
- BIOCHEMISTRY

DOGS — PARTIALLY NESTED AND CROSSED DESIGN

RATS — METHOD OF UNWEIGHTED MEANS

DUP050308453