THE EFFECT OF PROLONGED FEEDING OF LOW LEVELS OF LEAD TO LABORATORY ANIMALS

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I. INTRODUCTION

LITTLE EXPERIMENTAL WORK HAS BEEN DONE ON THE BIOLOGICAL EFFECTS OF LONG-TERM EXPOSURE TO LOW CONCENTRATIONS OF LEAD. RECENTLY, A COMPREHENSIVE STUDY ON THE CHRONIC TOXICITY OF ORALLY-ADMINISTERED LEAD IN LABORATORY ANIMALS WAS RELEASED BY THE AMERICAN PETROLEUM INSTITUTE (APRIL, 1971). THIS STUDY SHOWED THAT THE ADMINISTRATION OF LEAD ACETATE TO RATS, DOGS, AND MONKEYS FOR 22 MONTHS AT A DIETARY LEVEL OF 10 PPM AS LEAD PRODUCED NO EFFECTS THAT COULD BE DETECTED BY ANY OF THE TECHNIQUES THAT WERE EMPLOYED; 50 PPM PRODUCED MINIMAL EQUIVOCAL EFFECTS, AND 100 PPM PRODUCED HISTOLOGIC CHANGE WITHOUT FUNCTIONAL CHANGE IN THE KIDNEYS OF RATS. THE PRESENT STUDY WAS UNDERTAKEN TO FURTHER CLARIFY THE POSSIBLE BIOLOGIC MANIFESTATIONS OF LONG-TERM, LOW-LEVEL, DIETARY ADMINISTRATION OF LEAD IN LABORATORY ANIMALS.

II. METHODOLOGY

A. EXPERIMENTAL DESIGN

(SLIDE #1)

THE BASIC EXPERIMENTAL DESIGN CONSISTED OF TWO STUDIES. IN STUDY I, RATS AND DOGS WERE FED DIETS OF GROUND PURINA LAB CHOW TO WHICH WAS ADDED 0, 10, 50, 100,

AND 500 PPM LEAD ADMINISTERED AS LEAD ACETATE $Pb(C_2H_3O_2)_2 \cdot 3H_2O$. THE AMOUNT OF LEAD ADDED TO THE DIET WAS CALCULATED ON THE BASIS OF ACTUAL LEAD, THIS BEING 54.6% OF THE WEIGHT OF THE ACETATE.

BOTH MALES AND FEMALES OF EACH SPECIES WERE USED. THE VARIOUS BIOLOGIC INDICES UNDER OBSERVATION WERE MEASURED AT 10 DIFFERENT INTERVALS THROUGHOUT THE TWO YEARS OF FEEDING.

(SLIDE #2)

AFTER STUDY I HAD BEEN IN PROGRESS FOR SEVERAL MONTHS, IT APPEARED THAT A DIETARY LEVEL OF 500 PPM LEAD WAS NOT AFFECTING THE CLINICAL, NUTRITIONAL, OR REPRODUCTIVE INDICES OF RATS. THEREFORE, A SECOND TWO-YEAR FEEDING STUDY WAS INITIATED IN RATS TO PROVIDE DIETARY LEAD LEVELS OF 1000 AND 2000 PPM.

B. PARAMETERS UNDER OBSERVATION

THE NEXT THREE SLIDES WILL SHOW THE BIOLOGIC RESPONSES WHICH WERE OBSERVED OR MEASURED PERIODICALLY THROUGHOUT THE TWO YEARS OF DIETARY LEAD ADMINISTRATION.

(SLIDE #3)

1. Clinical Observations

The animals were observed for various gross aspects of appearance and behavior. Dogs were given a neurological examination initially and at one and two years of feeding. Weight gain, food consumption, and incidence of mortality were also recorded for all test groups.

2. Lead Analyses

Blood, urine, feces, and various tissues were periodically analyzed for lead in all dogs and in four to six rats selected at random at each dietary lead level. Also, test diets for all groups were analyzed periodically for their actual lead content.

(SLIDE #4)

3. Hematology

Hematologic examination of both rats and dogs included a complete blood count, hematocrit, hemoglobin, and number of basophilic stippled cells.

4. Biochemistry

Biochemical analyses involved an evaluation of liver function, a complete urinalysis, and special tests to

DETERMINE DELTA-AMINOLEVULINIC ACID (DALA) IN URINE AND DELTA-AMINOLEVULINIC ACID DEHYDRASE (ALA-D) IN BLOOD IN BOTH RATS AND DOGS.

(SLIDE #5)

5. PATHOLOGY

ALL ANIMALS THAT WERE SACRIFICED, DIED, OR SURVIVED TWO YEARS OF DIETARY LEAD RECEIVED A THOROUGH NECROPSY. ALL MAJOR ORGAN SYSTEMS WERE EXAMINED, BOTH GROSSLY AND MICROSCOPICALLY.

6. THREE-GENERATION REPRODUCTION STUDY IN RATS

A THREE-GENERATION, SIX-LITTER REPRODUCTION STUDY WAS CARRIED OUT ON RATS RECEIVING 0, 10, 50, 100, 1000, AND 2000 PPM DIETARY LEAD (Pb). CRITERIA EVALUATED INCLUDED VARIOUS INDICES OF REPRODUCTION AND LACTATION, THE AVERAGE BODY WEIGHT OF WEANLINGS, AND A HISTOLOGICAL EVALUATION OF 21-DAY OLD WEANLINGS.

C. STATISTICAL ANALYSIS

THE DATA FROM EACH RAT STUDY AND FROM THE DOG STUDY WERE SUBJECTED, RESPECTIVELY, TO AN ANALYSIS OF VARIANCE TO DETERMINE THE SIGNIFICANT EFFECT OF THREE VARIABLES (DIETARY LEAD,

SEX, AND TIME) ON THE VARIOUS QUANTITATIVE RESPONSES WHICH WERE MEASURED DURING THE TWO YEARS OF DIETARY LEAD ADMINISTRATION.

III. RESULTS

FOR THE PURPOSE OF THIS PRESENTATION, I WILL DEAL MAINLY WITH THE SIGNIFICANT EFFECTS OF ONE VARIABLE - DIETARY LEAD - ON THE VARIOUS BIOLOGIC RESPONSES THAT WERE MEASURED.

(SLIDE # 6)

A. CLINICAL OBSERVATIONS

THERE WAS NO SIGNIFICANT EFFECT ON APPEARANCE, BEHAVIOR, NEUROLOGICAL EXAMINATION, BODY WEIGHT, OR MORTALITY IN DOGS RECEIVING AS MUCH AS 500 PPM PB IN THEIR DIETS.

IN RATS RECEIVING AS MUCH AS 2000 PPM DIETARY LEAD, INDICES OF APPEARANCE AND BEHAVIOR WERE NORMAL. HOWEVER, THE PRESENCE OF 1000 AND 2000 PPM LEAD IN THE DIET APPEARED TO DEPRESS THE RATE OF WEIGHT GAIN IN BOTH MALE AND FEMALE RATS. ALSO, AN INCREASE IN MORTALITY WAS SEEN IN MALE RATS FED 500 PPM LEAD AND ABOVE.

B. Lead Analyses

(SLIDE #7)

This time graph shows the patterns of blood lead concentrations in dogs at different dietary lead levels. There was a significant trend toward higher blood lead values over the two years of lead feeding. Also, a highly significant relationship ($P < 0.01$) was found between blood lead and dietary lead. The blood and urine lead levels of dogs receiving 10 ppm or more lead (P_B) in the diet were significantly greater than the control values. Similar results were found in the rat data.

(SLIDE #8)

On this slide we see that the lead content of bone, blood, liver, kidney, and brain in the dog increased as the amount of lead in the diet increased. The relative rate of increase was greatest for liver lead and least for bone lead. In rats, similar results were found except that the kidney, rather than the liver, showed the sharpest rate of increase.

(SLIDE #9)

THERE WERE SIGNIFICANT CORRELATIONS BETWEEN TISSUE LEAD LEVELS AND BLOOD LEAD LEVELS. FOR EXAMPLE, THIS SLIDE SHOWS THE CORRELATION BETWEEN KIDNEY LEAD CONCENTRATION AND BLOOD LEAD LEVELS IN DOGS. A COEFFICIENT OF CORRELATION (R) OF 0.88 INDICATES THAT >77.0% OF THE VARIATION IN KIDNEY LEAD CAN BE ACCOUNTED FOR BY BLOOD LEAD. THE LEAD CONTENT OF BONE, LIVER, BRAIN, AND KIDNEY WAS SIGNIFICANTLY CORRELATED WITH BLOOD LEAD IN ADULT DOGS AND ALSO IN RATS FED OVER A LIFETIME. THIS INDICATES THAT THE BLOOD LEAD IS A GOOD INDEX OF TISSUE DEPOSITION AS WELL AS EXPOSURE.

(SLIDE #10)

THERE WERE NO SIGNIFICANT HEMATOLOGIC EFFECTS IN DOGS EXCEPT FOR AN INCREASE IN THE NUMBER OF STIPPLED CELLS SEEN AT 500 PPM. IN RATS, A STATISTICALLY SIGNIFICANT INCREASE IN STIPPLED CELLS WAS SEEN AT 10 PPM AND ABOVE AND A DECREASE IN HEMOGLOBIN CONCENTRATION AND HEMATOCRIT WAS NOTED ONLY AT DIETARY LEAD LEVELS OF 1000 PPM AND ABOVE.

THE LIVER FUNCTION TESTS PERFORMED AND THE RESULTS OF URINALYSIS WERE WITHIN NORMAL LIMITS IN DOGS RECEIVING

AS MUCH AS 500 PPM LEAD OR IN RATS RECEIVING AS MUCH AS 2000 PPM LEAD IN THE DIET.

(SLIDE #11)

ON THIS SLIDE WE SEE THAT LEAD DID INHIBIT ALA-D ACTIVITY AT A CONCENTRATION OF 50 PPM IN RATS AND 100 PPM IN DOGS. HOWEVER, THIS INHIBITION WAS NOT ASSOCIATED WITH ANY INCREASED URINARY EXCRETION OF ITS SUBSTRATE DALA UNTIL A CONCENTRATION OF 500 PPM LEAD (P_B) WAS ADMINISTERED IN THE DIET. THESE FINDINGS ARE CONSISTENT WITH THE FUNCTIONAL RESERVE EXHIBITED IN MANY BIOLOGICAL SYSTEMS.

SIGNIFICANT CORRELATIONS WERE ALSO FOUND BETWEEN ALA-D ACTIVITY AND BLOOD LEAD, AND BETWEEN DALA AND BLOOD LEAD IN BOTH RATS AND DOGS. THESE RELATIONSHIPS WERE VERY SIMILAR TO THOSE DESCRIBED BY HERNBERG FOR HUMANS.

(SLIDE #12)

THERE WERE NO PATHOLOGIC EFFECTS OF DIETARY LEAD ON ANY ORGAN SYSTEM IN FEMALE DOGS FED 500 PPM LEAD OR LESS.

IN MALE DOGS, HISTOLOGY WAS NEGATIVE EXCEPT FOR A SLIGHT DEGREE OF CYTOMEGALY FOUND IN THE PROXIMAL CONVOLUTED TUBULES OF THE KIDNEY IN TWO OUT OF FOUR DOGS FED 500 PPM LEAD.

IN RATS, THERE WAS NO PATHOLOGIC EFFECT OF DIETARY LEAD ON ANY ORGAN SYSTEM AT LEAD LEVELS UP TO AND INCLUDING 100 PPM. AT 500 PPM LEAD AND GREATER IN THE DIET, BOTH MALE AND FEMALE RATS SHOWED HISTOLOGIC LESIONS ATTRIBUTABLE TO LEAD IN THE KIDNEY. AT THREE MONTHS OF FEEDING AT 500 PPM, RATS SHOWED CYTOMEGALY, INTRANUCLEAR INCLUSIONS, AND CYTOPLASMIC PIGMENTATION IN THE PROXIMAL CONVOLUTED TUBULE OF THE KIDNEY. AT 12 MONTHS OF FEEDING, ADDITIONAL CHANGES OCCURRED SUCH AS METAPLASIA AND HYPERPLASIA.

KIDNEY TUMORS WERE ALSO FOUND IN MALE RATS FED 500 PPM OR MORE LEAD (P_B). THESE TUMORS WERE FIRST OBSERVED AT 14 MONTHS WHEN A RAT RECEIVING 2000 PPM LEAD DIED. TUMORS AT LOWER LEVELS WERE DISCOVERED AT TIME OF SACRIFICE (24 MOS.).

(SLIDE #13)

THE INCIDENCE OF SUCH KIDNEY TUMORS IN RATS AT 500 PPM LEAD AND ABOVE IN THEIR DIETS IS SHOWN IN THIS TABLE.

IT IS SEEN THAT THE INCIDENCE OF KIDNEY TUMORS INCREASES IN MALE RATS FROM 10% AT 500 PPM DIETARY LEAD, TO 50% AT 1000 PPM, TO 80% AT 2000 PPM. FEMALE RATS SHOWED NO KIDNEY TUMORS UNTIL A DIET CONTAINING 2000 PPM LEAD WAS ADMINISTERED. MOST OF THE TUMORS WERE CONSIDERED TO BE ADENOMAS DERIVED FROM THE TUBULAR EPITHELIUM. THE GREATER SUSCEPTIBILITY OF THE MALE RAT TO KIDNEY TUMORS FROM LEAD MAY BE RELATED TO THE HIGHER INCIDENCE OF SPONTANEOUS CHRONIC NEPHRITIS IN MALE RATS OF THIS STRAIN AS COMPARED TO FEMALES.

(SLIDE #14)

THE RESULTS OF THE THREE-GENERATION, SIX-LITTER REPRODUCTION STUDY ON RATS ARE SHOWN ON THIS SLIDE. THERE WERE NO MAJOR DIFFERENCES BETWEEN CONTROL AND TEST GROUPS WITH RESPECT TO REPRODUCTION AND LACTATION INDICES IN RATS FED UP TO AND INCLUDING 2000 PPM LEAD (P_B).

AT 1000 AND 2000 PPM DIETARY LEAD, HOWEVER, THE AVERAGE WEIGHT OF WEANLING RATS WAS SLIGHTLY DECREASED. ALSO, HISTOLOGIC EXAMINATION OF ALL ORGAN SYSTEMS IN THE 21-DAY OLD WEANLING RATS (F_3B) REVEALED LESIONS IN THE

KIDNEY ATTRIBUTABLE TO LEAD AND COMPARABLE TO THOSE PREVIOUSLY FOUND IN ADULT RATS RECEIVING 500 PPM LEAD OR MORE IN THEIR DIETS. SINCE WEANLING RATS DERIVE MOST OF THEIR NOURISHMENT FROM SUCKLING IN THE FIRST THREE TO FOUR WEEKS AFTER BIRTH, IT IS ASSUMED THAT LEAD WAS TRANSMITTED TO THE NEWBORN THROUGH THE MILK, RESULTING IN HISTOLOGIC CHANGES IN THE KIDNEY.

SUMMARY

(SLIDE #15)

IN SUMMARY, THIS STUDY SHOWED THAT THE INGESTION OF 10 PPM LEAD (P_B) BY RATS AND DOGS RESULTED IN A DETECTABLE INCREASE IN BLOOD, URINE, AND KIDNEY LEAD LEVELS; HOWEVER, NO EFFECT ON CLINICAL OR BIOCHEMICAL PARAMETERS WAS SEEN AT THIS DIETARY LEVEL. AT 50 PPM LEAD (P_B) IN THE DIET OF RATS, AND 100 PPM IN DOGS, A SIGNIFICANT DECREASE IN ALA-D ACTIVITY OCCURRED. THIS DECREASE WAS NOT ASSOCIATED WITH A CORRESPONDING INCREASE IN THE EXCRETION OF DALA, THE SUBSTRATE FOR ALA-D. IN OTHER WORDS, ALTHOUGH ALA-D ACTIVITY WAS INHIBITED, SUFFICIENT ENZYME RESERVE REMAINED TO HANDLE THE BODY'S REQUIREMENTS.

(SLIDE #16)

IT WAS NOT UNTIL THE DIET CONTAINED 500 PPM LEAD (PB) THAT ANIMALS DID SHOW A SIGNIFICANT INCREASE IN DALA EXCRETION. ALSO, AT 500 PPM DIETARY LEAD AND ABOVE, KIDNEY TUMORS AND AN INCREASE IN MORTALITY WERE SEEN IN RATS.

EVIDENCE OF DEPRESSED HEMOGLOBIN, HEMATOCRIT, AND WEIGHT GAIN WERE NOT FOUND UNTIL RATS WERE FED DIETS CONTAINING 1000 PPM LEAD (PB) OR MORE. INDICES OF REPRODUCTION AND LACTATION WERE NORMAL AT ALL DIETARY LEVELS TESTED. HOWEVER, A DEPRESSED WEIGHT GAIN AND RENAL LESIONS WERE FOUND IN THE WEANLING RATS OF PARENTS INGESTING 1000 PPM LEAD (PB) OR MORE IN THE DIET.

RESULTS FROM THIS STUDY CAN BE INTERPRETED IN TWO WAYS. FIRST, ONE COULD SAY THAT SUCH INFORMATION COULD NOT BE EXTRAPOLATED TO THE HUMAN SITUATION BECAUSE THE DOSES OF LEAD FED TO BOTH RATS AND DOGS WERE MUCH HIGHER THAN THE DAILY DIETARY LEAD INTAKE OF HUMANS. FOR EXAMPLE, A LEVEL OF 10 PPM PB FED TO RATS AND DOGS IS 70 TIMES HIGHER THAN DAILY HUMAN DIETARY INTAKE, IF DOSE IS CALCULATED ON THE BASIS OF µG PB/KG BODY WEIGHT.

(SLIDE #17)

HOWEVER, THE RESULTS SHOWN ON THIS TABLE SUGGEST ANOTHER POSSIBLE INTERPRETATION. HERE, WE SEE THE BLOOD, KIDNEY, AND BONE LEAD LEVELS IN DOGS AND RATS AFTER 24 MONTHS OF FEEDING. THE NORMAL RANGE OF LEAD CONCENTRATION IN THE SAME TISSUES IS ALSO SHOWN FOR HUMANS.

IT IS INTERESTING THAT AT 100 PPM DIETARY LEAD AND BELOW, BLOOD LEAD LEVELS AS WELL AS KIDNEY AND BONE LEAD LEVELS, IN RATS AND DOGS ARE COMPARABLE TO HUMAN TISSUE LEAD LEVELS. IN THIS NORMAL RANGE OF BLOOD LEAD FOR HUMANS (11-40), INVESTIGATORS HAVE REPORTED A SIGNIFICANT DECREASE IN ALA-D ACTIVITY; IN THIS STUDY, WE SAW A SIGNIFICANT DECREASE IN ALA-D ACTIVITY AT A BLOOD LEAD OF 31.5 IN THE DOG AND AT 35.9 IN THE RAT.

ALSO, IN HUMANS, A BLOOD LEAD OF 80 µG/100 ML IS THE LEVEL AT WHICH CLINICAL SIGNS OF LEAD POISONING BEGIN TO APPEAR IN HUMANS. IN OUR STUDY, 500 PPM DIETARY LEAD IN RATS AND DOGS PRODUCED A SIGNIFICANT INCREASE IN DALA EXCRETION IN THE URINE; THE BLOOD LEAD CONCENTRATION IN BOTH SPECIES WAS ABOUT 80 µG/100 ML. ALSO, AT 500 PPM ($\approx$ 80 µG/100 ML-BLOOD LEAD), RATS BEGAN TO SHOW HISTOLOGICAL CHANGES IN THE KIDNEY ATTRIBUTABLE TO LEAD, AND AN INCREASE IN MORTALITY. KIDNEY LEAD LEVELS AND BONE LEAD LEVELS IN RATS FED 500 PPM LEAD ARE SEEN TO BE WELL ABOVE

THE LEVELS OF LEAD REPORTED IN THE KIDNEY AND BONE OF HUMANS.

THUS, ANOTHER INTERPRETATION FROM THE PRESENT ANIMAL STUDY IS THAT RESULTS DO SUPPORT SOME ASPECTS OF LEAD TOXICITY WHICH HAVE ALREADY BEEN REPORTED ON HUMANS.

HJT/JTD
5/5/72

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.

SLIDE #1

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CONTINUED

EXPERIMENTAL DESIGN

STUDY II

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.

SLIDE #2

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.)

SLIDE #3

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)

SLIDE #4

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

SLIDE #5

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

SLIDE #6

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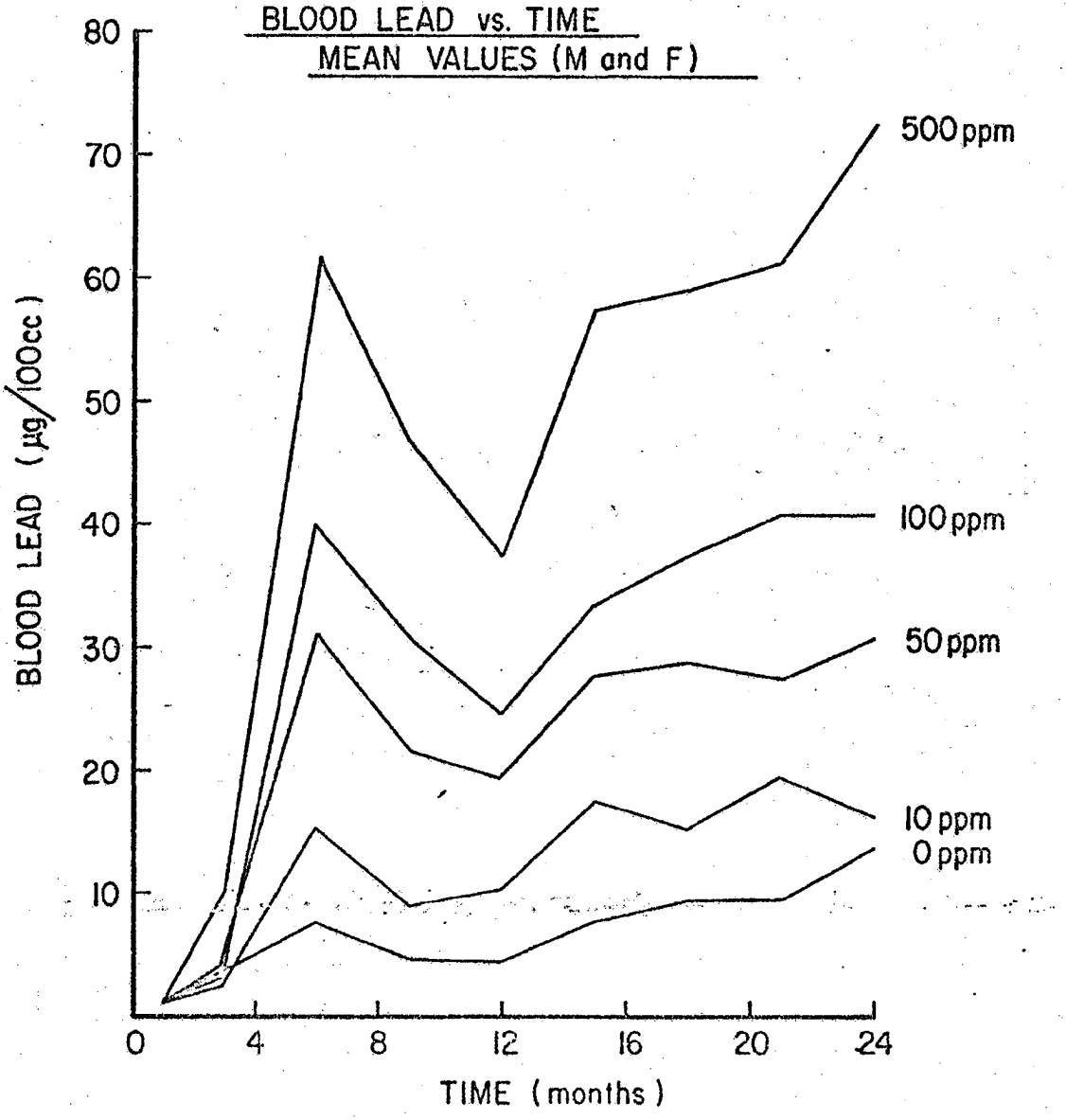
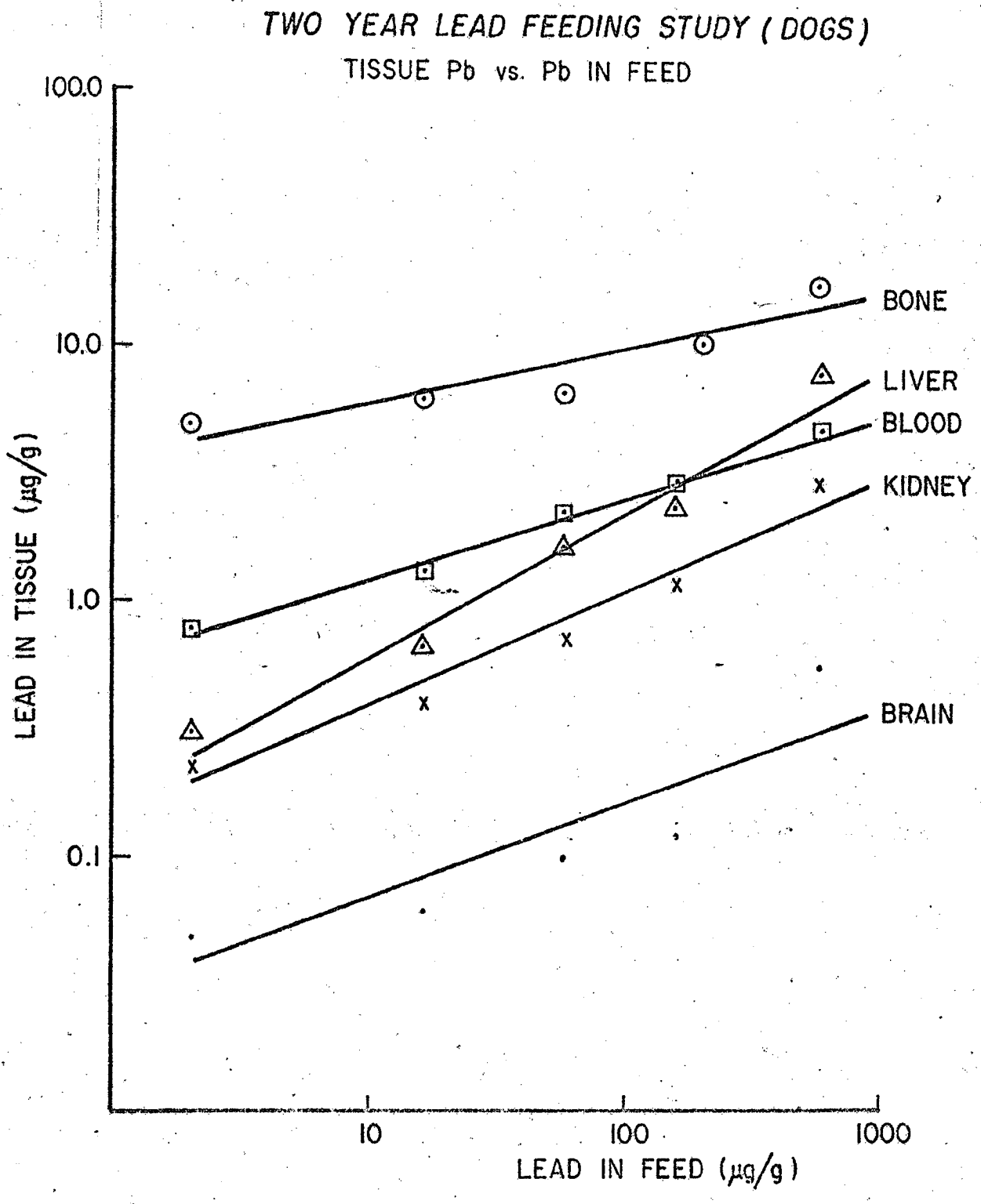
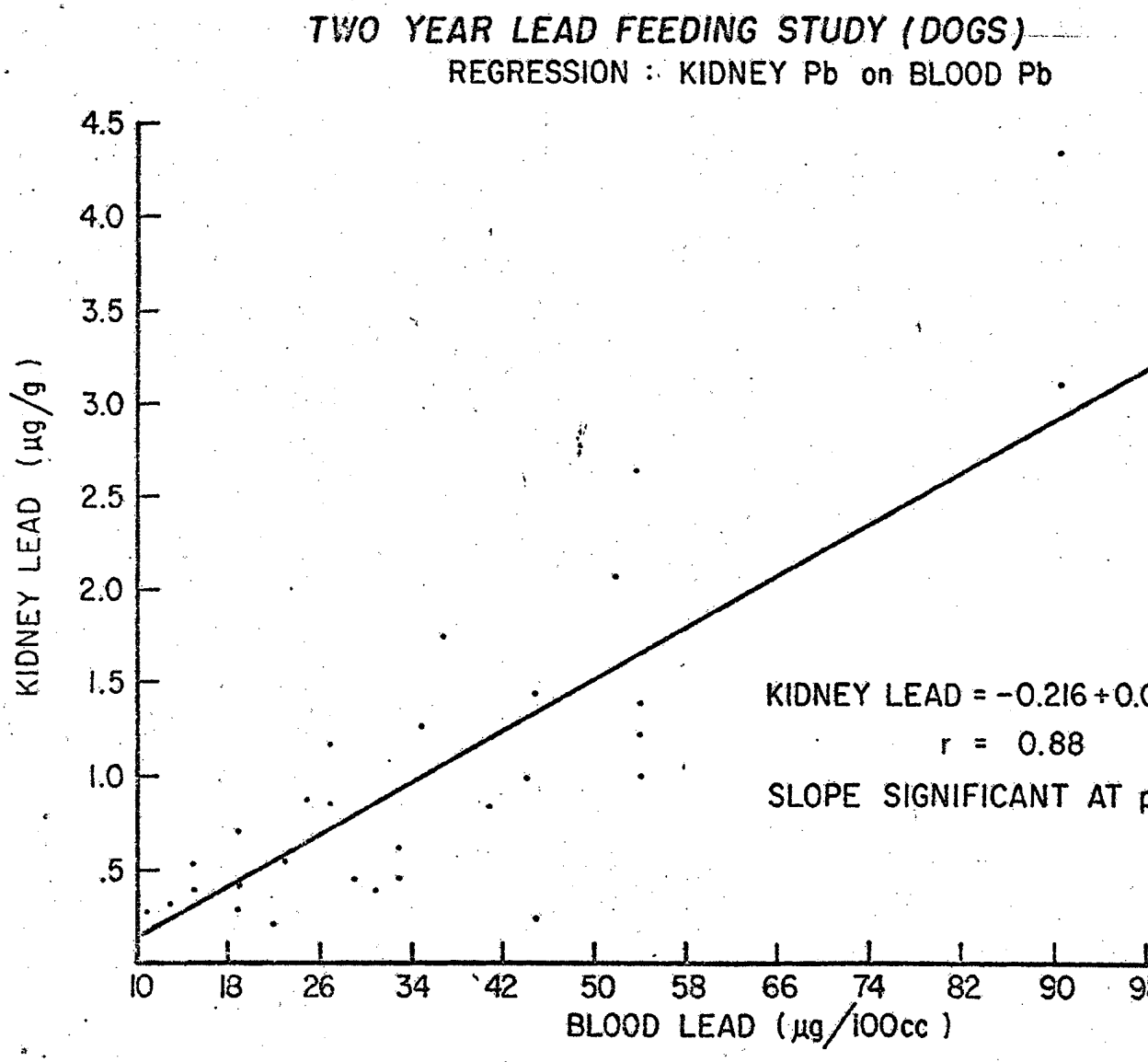
TWO YEAR LEAD FEEDING STUDY IN DOGS



SLIDE #8





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 $p < 0.05$.

SLIDE #10

EFFECT OF DIETARY Pb ON DALA AND ALA-D

MEAN VALUES (M & F)

DIETARY Pb LEVEL (ppm)	RATS		DOGS	
	DALA[1]	ALA-D[2]	DALA	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 $p < 0.05$.

SLIDE #11

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.

SLIDE #12

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

SLIDE #13

RESULTS OF THREE-GENERATION REPRODUCTION STUDY IN RATS

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

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

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 (↓)

SLIDE #14

SUMMARY TWO-YEAR LEAD FEEDING STUDY (RATS & DOGS)

SIGNIFICANT EFFECTS OF DIETARY LEAD

DOSE LEVEL	DOGS	RATS
0	NONE	NONE
10	↑ Pb IN BLOOD, URINE, FECES, LIVER AND KIDNEY	↑ Pb IN URINE, FECES, AND KIDNEY ↑ STIPPLED CELLS
50	↑ Pb IN BRAIN	↑ Pb IN BLOOD, BONE, BRAIN, AND LIVER ↓ ALA-D
100	↓ ALA-D	" " "

SLIDE #14

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CONTINUED

SUMMARY · TWO-YEAR LEAD FEEDING STUDY (RATS & DOGS)

SIGNIFICANT EFFECTS OF DIETARY LEAD

DOSE LEVEL	DOGS	RATS
500	↑ Pb IN BONE ↑ DALA AND STIPPLED CELLS	↑ MORTALITY (♂) KIDNEY CHANGES AND TUMORS (♂) ↑ DALA
1000	———	↓ Hb AND Hct. ↓ WT. GAIN IN ADULTS ↓ WT. OF WEANLINGS KIDNEY LESIONS OF WEANLINGS
2000	———	KIDNEY TUMORS (♀)

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SLIDE #16

PB LEVELS IN BLOOD, KIDNEY, AND BONE
(MEAN VALUES AT 24 MOS.)

DIETARY Pb (ppm)	BLOOD Pb (µg/100 ml)		KIDNEY Pb (µg/g)		BONE (µg/g
	DOG	RAT	DOG	RAT	DOG R
0	15.8	12.5	0.2	0.4	4.9
10	16.7	11.1	0.4	0.3	6.2
50	31.5	18.8	0.7	0.9	6.4 1
100	42.6	35.9	1.2	2.7	10.4 2
500	80.4	78.4	2.9	15.1	17.4 1
HUMAN (NORMAL RANGE)	11-40		0.3-1.4		4.7-5