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TAR-4123

004173

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

DATE: 12/27/84

SUBJECT: Reviews Of The 2-Year Feeding/Oncogenicity In Rats And 1-Year Feeding In Dogs For COMMAND.

TO: Robert Taylor, PM#25
Registration Division (TS-767)

FROM: Carolyn Gregorio, Toxicologist CAG 12-26-84
Toxicology Branch/ HED (TS-769)

THRU: Robert P. Zendzian, Ph.D. 12/26/84
Acting Section Head/ Section III
and
Ted Farber, Ph.D. T.M. Farber 12/27/84
Branch Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

Chemical: COMMAND, FMC 57020, Dimethazone

Caswell No.: 463D

Petitioner: FMC Corporation

Petition No.: 4F3128

Accession No.: 072774 through 072796; 072828; 073009

Background: The data submitted to support the Petitioner's request for a Temporary Tolerance on soybeans were not sufficient because a NOEL was not established in the rodent (rat and mouse) and nonrodent (dog) subchronic feeding studies. The Petitioner subsequently submitted data to support their request for a Permanent Tolerance (4F3128). It was decided

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in a meeting with Mr. Campt (meeting held September 20, 1984; attended by Mr. John Melone, Mr. James Ackerman, Mr. William Burnam, Dr. Robert Zendzian) that the Branch would reevaluate the Petitioner's Temporary Tolerance request in the following manner: (1.) complete a review of the 2-year feeding/onco study in rats and 1-year feeding study in dogs and (2.) peruse the Petitioner's submitted SUMMARIES for all the data submitted in the Permanent Tolerance request for any adverse or suspicious effects in other toxicological areas.

DATA SUMMARY

1.) 2-Year Feeding/Onco Study - Rats (FMC Study No. A81-650, Toxigenics Study No. 410-0816).

This study was approaching the limits of good practice due to the small number of survivors, especially in male groups, at the termination of the study. Mortality incidence coupled with the numerous intermediate sacrifices left 16, 26, 25, 19, 26, 19 survivors (out of 120 animals started in the study) for the 0, 20, 100, 500, 1000, 2000 ppm males, respectively at 24 months. According to acceptable study practices, survival in any group should not fall below 25% at final sacrifice.

Histopathological examination of the individual animal data demonstrated a non-statistical increase in pheochromocytomas and hepatocellular ademonas in male treatment groups between 18 and 24 months when compared to concurrent controls (Table 1.).

Table 1. Histopatholoy Of Selected Lesions In Male Rats

Dose (ppm)	0	20	100	500	1000	2000
Pheochromoctoma						
- 18 month*	0/23	1/15	0/16	1/17	0/18	1/20
- 24 month*	0/37	3/45	0/44	3/43	5/42	3/40
	0/60	4/60	0/60	4/60	5/60	4/60
Hepatocellular Adenoma						
- 18 month*	0/23	1/15	0/16	1/17	0/18	1/20
- 24 month*	1/37	4/45	1/44**	6/43	0/42	2/40
	1/60	5/60	1/60	7/60	0/60	3/60

* The denominator is a combination of scheduled sacrificed animals and early death animals.

** This group also had one (1) hepatocellular carcinoma.

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As requested, the Petitioner has submitted historical control data from Toxigenics (2 studies for pheocromocytoma, 1 study for liver lesions; letter from Cuirle [FMC] to Taylorl [EPA], dated December 6, 1984).

The Branch's Peer Review Group (Dr. Ted Farber, Dr. Reto Engler, Mr. Bert Litt, Mr. Bill Burnam, Dr. Robert Zendzian) met on December 21, 1984 to discuss the biological relevance of the above reported tumor types. The group unaminiously agreed that no dose reponse relationship was observed, that a more than adequate dose spread was employed in this study, that the historical control data submitted indicate a high degree of variability in the incidence of these types of tumors, and that the low incidence observed in the concurrent controls of this study was within the range of variability. Therefore, based on these facts, the incidence of pheocromocytoma and hepatocellular adenoma observed in this study are not considered to indicate oncogenic potential.

Systemic NOEL = 100 ppm (calculated 4.3 mg/kg/day)
Systemic LEL = 500 ppm (calculated 21.5 mg/kg/day)

No Oncogenic Potential Observed.

2.) 1-Year Feeding - Dog (FMC Study No. A82-758, HRI Study No. 6124100; dated October 25, 1983).

An increase in cholesterol and liver weights (absolute and relative to body weight) were observed in the 2500 and 7500/5000 ppm males and females when compared to concurrent controls throughout the study.

NOEL = 500 ppm (12.5 mg/kg/day)
LEL = 2500 ppm (62.5 mg/kg/day)

SUMMARY FOR OTHER TOXICOLOGY AREAS REGARDED WITH CONCRN

1.) 24-Month Feeding/Onco - Mouse (FMC Study No. A81-651; Toxigenics Study No. 410-0817).

In perusing the Petitioner's submitted "summary", it was deemed necessary to review the histopathological portion of the study with regard to liver pathology (Table 2). No other portions of this study have been reviwed.

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Table 2. Liver Histopathology In Male Mice Over 24 Months

Dose (ppm)	0	20	100	500	1000	2000
Hepatocellular Adenoma						
6-12 month*	2/12	1/17	1/18	1/14	2/14	0/14
12-18 month*	2/19	1/20	1/20	0/19	0/20	0/19
18-24 month*	10/36	7/31	8/31	8/37	7/35	8/36
	14/67	9/68	9/69	9/70	9/69	8/69
Hepatocellular Carcinoma						
6-12 month*	0/12	0/17	2/18	0/14	0/14	0/14
12-18 month*	1/19	2/20	0/20	2/19	5/20	1/19
18-24 month*	2/36	1/31	7/31	5/37	5/35	2/36
	3/67	3/68	9/69	7/70	10/69	3/69
TOTAL HEPATOCELLULAR ADENOMA AND CARCINOMA						
	17/67	12/68	19/69	16/70	19/69	11/69
Hepatocellular Cytomegaly						
3 month	0/19	3/20	-	0/20	-	3/20
6 month	0/10	0/10	0/10	0/10	2/10	5/10
6-12 month*	0/12	0/17	0/18	0/14	2/14	0/14
12-18 month*	0/19	0/20	2/20	2/19	1/20	4/19
18-24 month*	1/36	0/31	1/31	0/37	0/35	4/36
TOTAL HEPATOCELLULAR CYTOMEGALY						
	1/96	3/91	3/89	2/100	5/89	12/99

* The denominator is a combination of scheduled sacrifice and early death animals.

- Not reported

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The Branch's Peer Review Group discussed the liver pathology data set at the same meeting mentioned previously in this memo. The Group aggreed that the data presented indicated liver toxicity as evidenced by the incidence of hepatocellular cytomegaly throughout the study. With regard to the incidence of liver tumors, the Group agreed that there was no dose response relationship observed and that additively (sum of hepatocellular adenoma and hepatocellular carcinoma) do not demonstrate an oncogenic trend. Combination of benign and malignant tumors generally represent the histogenetic development of the tumors and adding them together minimizes the effect of pathologists using different terminology. Therefore, based on these facts, the liver pathology observed in this study are not considered to indicate an oncogenic potential.

LISTING OF STUDIES FOR WHICH PETITIONER SUMMARY WAS SURVEYED

1.) Teratology - rabbit (FMC Study No. A81-655, WIL Research Report No. 81157; dated September 14, 1982).

2.) Teratology - rat (FMC Study No. A83-1142; dated June 29, 1984)

3.) 2-Generation Reproduction - rat (FMC Study No. A82-757, Toxigenics Study No. 450-1095; dated June 12, 1984).

4.) Metabolism - Rat Balance Study and Tissue Ditribution of Methylene 14C-Labeled (FMC Report No. PC-0017, PRI Syudy No. FM-124r; dated March 22, 1984).

5.) Metabolism of Methylene-14C FMC 57020 - rat (FMC Report No. P-0898; dated June 18, 1984).

6.) Identification Of Metabolites In Urine And Feces of Rats Dosed With 14C-FMC 57020 (FMC Report No. P-0897; dated June 14, 1984).

7.) Mutagenicity - HGPRT Assay (CHO Cells) (FMC Report No. A83-1143; Microbiological Associates Study No. T2198-332; dated June, 1984).

8.) Mutagenicity - Ames Test (FMC Study No. A84-1189, MA Study No. T2423-501; dated May, 1984).

9.) Mutagenicity - Ames Test (FMC Report No. A83-864, Hazleton Study No. 104-211; dated July, 1983).

10.) Mutagenicity - Ames Test (FMC Report No. A83-1111; MA Study No. T2176-501; dated January, 1984).

11.) Mutagenicity - HGPRT Assay (FMC Report No. A84-1188, MA Study No. T2422-332; dated July, 1984).

12.) Mutagenicity - Ames (FMC Study No. A84-1281; dated June, 1984).

TEMPORARY TOLERANCE ASSESSMENT

The Petitioner has submitted a Petition for a Temporary Tolerance (4G2987), for use of COMMAND in/on soybeans. The Petitioner has based the request on residue levels not to exceed 0.05 ppm. The Residue Chemistry Branch has indicated that no secondary residues in meat, milk, poultry, or eggs is expected (memo Worthington to Taylor, dated September 24, 1984). Therefore, the tolerance assessment is based on the proposed residue in or on soybeans ONLY.

The % ADI (0.043) is based on the 2-year feeding/oncogenicity study in rats (NOEL = 4.3 mg/kg/day; Safety Factor = 100). The portion of the % ADI used by establishing this tolerance in or on soybeans (based on the residue level of 0.05 ppm) would be 0.03%. See attached printout.

RECOMMENDATION

The toxicology data base is sufficient to recommend establishing a Temporary Tolerance in or on soybeans.

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40 CFR NUMBER CS FILE 12/5/84

File last updated 12/5/84

ACCEPTABLE DAILY INTAKE DATA **DRAFT**

RAT,Older	NOEL	S.F.	ADI	TPI
mg/kg	PPM		mg/kg/day	mg/day(60kg)
4.300	430.00	100	0.0430	2.5800

Current Action 4C2987

NOEL not recorded

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Soybeans (oil)(148)	0.050	0.2	0.00069

TPI	THRC	% ADI
2.5800 mg/day(60kg)	0.0007 mg/day(1.5kg)	0.03

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Compound: Command (FMC 57020), dimethazone

Formulation: Technical (88.8% Purity; Reassayed as 91.4%)
Batch No. E156-146

Citation: 90-Day Subchronic Toxicity Dietary And 24-Month Chronic Toxicity And Oncogenicity Dietary Study In Rats Utilizing FMC 57020 Technical. FMC Study No. A81-650, Toxigenics Study No. 410-0816. July 10,1984. Report preparation by Leslie D. Morrow. Report approval by Dale A. Mayhew. Quality assurance provided by William D. Barta, Walter L. Bullock and Donald G. MacKellar.

Accession Number: 072774 through 072796; 073009

Reviewed by: Carolyn Gregorio, Toxicologist CDG 12-27-84 12/27/84
Toxicology Branch/HED (TS-769)

Core Classification: Minimum

Toxicity Category: Not applicable

Conclusion: In this study, the mortality incidence coupled with the numerous intermediate sacrifices (10/sex/dose at 1, 2, 6, 12, 18 months; 20/sex/dose at 3 months) was approaching the minimum limits of an acceptable study for all groups (see Table 1 and 2 for numbers of survivors). In addition, although a slight elevation in cholesterol, liver to body weight ratio and liver to brain weight ratio was observed in the 500, 1000 and 2000 ppm females, there were no other systemic indications of possible treatment related effects.

Histopathology examination of individual animal data demonstrated a non-statistical increase in pheochromocytomas and hepatocellular ademonas in male treatment groups between 18 and 24 months when compared to concurrent controls (Table 6). As requested, the Petitioner has submitted historical control data from Toxigenics ([2 studies for pheocromocytoma, 1 study for liver pathology]; letter from Curirle [FMC] to Taylor [EPA], dated December 21, 1984; letter attached to to this review).

The Toxicology Branch's Peer Review Group (Dr. Ted Farber, Dr. Reto Engler, Dr. Robert Zendzian, Mr. Bert Litt, Mr. William Burnam) met on December 21, 1984 to discuss the biological relevance of the above mentioned tumor types. The group unaminiously agreed that no dose response relationship was observed, that a more than adequate dose spread was employed in this study, that the historical control data submitted indicate a high degree of variability in the incidence of these types of tumors, and that the low incidence observed in the concurrent controls was within the range of variability. Therefore, based on these facts, the incidence of pheochromocytoma and hepatocellular adenoma observed in this study do not represent an oncogenic potential.

Systemic NOEL = 100 ppm (calculated 4.3 mg/kg/day)
Systemic LEL = 500 ppm (calculated 21.5 mg/kg/day)

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No Oncogenic Potential Observed.

Homogeneity of Command in Mixed Diets: Homogeneity assays were reported for the 20, 1000 and 8000 ppm dose levels throughout the first 90 days of the study and the 20 and 2000 ppm doses subsequently for the remainder of the study. These values indicate acceptable homogeneity of the test compound in the tested diets throughout the study.

Stability of Command In Mixed Diets: Stability assays were reported for 7 and 14 days at ambient temperatures, refrigerated temperature (39°F) and frozen temperature (25o F). According to the authors, diets were prepared weekly and held frozen for 7 days before diet mixing was conducted. The assays show that the compound was stable in the diet mix for 14 days at frozen and refrigerated temperatures. However, the assay at 14 days for ambient temperature showed a -7.21%, -14.90%, -10.60%, -11.40%, -6.01%, 5.35 and -6.33% change for the 20, 100, 500, 1000, 2000, 4000 and 8000 ppm groups respectively. At 7 days, the assay for ambient temperature was in an acceptable range for all doses.

Materials and Methods: Sprague-Dawley outbred albino rats (28 days old) were recieved from the Charles River Breeding Laboratories. After a 2-week acclimation period, 120 animals/sex were assigned to the various dose groups. Command was administered in the diet at concentrations of 0, 20, 100, 500, 1000, 2000, 4000 and 8000 ppm. At 1 month, 2 month, 6 month, 12 month, and 18 month interim sacrifices, 10 animals/sex/dose were sacrificed. At 90 days 20 rats/sex/dose from the 0, 20, 500, 2000, and 8000 ppm groups were sacrificed. "Immediately following the 90-day sacrifice and after consideration of the relative organ/body weight ratio data, the remaining animals in the 4000 and 8000 ppm groups were removed from the study. Prior to sacrifice of the 4000 and 8000 ppm animals, 15 rats/sex in each of these groups were selected to comprise the recovery study."

"Fresh diets were prepared weekly and held frozen for approximately seven days.... Sufficient diet was offered at each feeding to assure one week's ad libitum feeding."

The following parameters were recorded throughout the study:

1. Clinical observations and mortality.

2. Body weights and food consumption.

3. Hematology (erythrocyte count, hematocrit, hemoglobin, total leukocyte count, differential leukocyte count, platelet count, reticulocyte count, cell indices (MCH, MCV, MCHC).

4. Blood chemistry (calcium, potassium, glutamic pyruvic transaminase, glutamic oxaloacetic transaminase, gamma glutamyic transferase, glucose, urea nitrogen, alkaline phosphatase, albumin, globulin, total protein, bilirubin [total and direct], cholesterol).

5. Urinalysis (specific gravity, pH, protein, glucose, ketones, blood, bilirubin, urobilinogen, microscopic elements).

6. Pathology for animals sacrificed at 1 and 2 months were discarded following gross examination.

7. Pathology for animals at 3, 6, 12, 18 and 24 months:

   a. Organ weights (brain, gonads, heart, kidneys, liver).

   b. Histology (adrenals, bone and bone marrow [femur], brain, pancreas, pituitary, prostate, salivary gland (mandibular), esophagus, eyes, gonads, harderian glands, heart, intestine,

kidneys, liver, lung and mainstem bronchi, skeletal muscle (rectus femoris) spleen, stomach, thymus, thyroid and parathyroids, trachea, urinary bladder, uterus, any lesions of uncertain nature and tissue masses with regional lymph nodes).

8. Additional tissues and organs from animals found dead, accidentally killed, sacrificed moribund at 6, 12, 18 an 24 months (lymph node [mesenteric], mammary gland, nerve (sciatic), skin, spinal cord [cervical and lumbar]).

RESULTS

Observations: The authors reported that "in animals for the two-year segment of this study, an increase in the number of females exhibiting palpable tissue masses, primarily of the ventral body surface, was noted."

Mortality: An increased incidence of early deaths was noted in all male groups (Table 1). The numerous scheduled sacrifices reduced the number of possible survivals substantially (a total of 70 animals/sex dose were scheduled for sacrifice) and was approaching the minimum limits of an acceptable study. Survival in any group should not fall below 25%.

Table 1. Survivors In Males Over Selected Sacrifice Times *

Dose (ppm)*	0	20	100	500	1000	2000
Month On Test						
0	120	120	120	120	120	120
3	79	80	80	80	80	80
6	68	70	69	70	70	70
12	57	59	59	58	58	59
18	36	42	41	39	41	39
24	16	26	25	19	26	19

Table 2. Survivors In Females Over Selected Sacrifice Times *

Dose (ppm)*	0	20	100	500	1000	2000
Month On Test						
0	120	120	120	120	120	120
3	80	80	80	80	80	80
6	69	70	70	70	70	70
12	58	58	60	58	59	58
18	33	42	42	41	42	41
24	23	29	29	25	25	30

* Doses 4000 and 8000 ppm were maintained only for the 3-month sacrifice.

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Body Weights: The 4000 and 8000 ppm males and females showed statistically significant lower mean body weights when compared to respective controls through week 15 of the study, when these dose groups were terminated.

Slightly lower mean body weights were observed in the 2000 ppm males and 1000 and 2000 ppm females throughout the 103 weeks of the study. However these weights were not 10% lower than respective controls and therefore not considered significant.

Food Consumption: The 4000 and 8000 ppm males and females showed decreased lower mean food consumption when compared to respective controls through week 15 of the study, when these dose groups were terminated. These data are consistent with the observed lower body weight gains observed in these groups and appear to represent a palatability problem with the test substance at these doses.

Mean food consumption values were similar for all other male and female groups throughout the 103-week study. In concert with the mean food consumption, mean test article consumption is as follows (Table 3):

Table 3. Mean Compound Consumption Over 103 Weeks*

Dose (ppm)	0	20	100	500	1000	2000
Females mg/kg/day	0	1.1	5.5	27.8	56.5	112.9
Males mg/kg/day	0	0.9	4.3	21.5	42.9	84.8

* This Table is abstracted from Registrant's submission.

Hematology: Mean hematology values were similar for all groups throughout the study.

Clinical Chemistry: Mean clinical chemistry values were similar for all male groups thoughout the study except for a statistically significant elevation of cholesterol at the 8000 ppm dose through 3 months (dose terminated at 3-month sacrifice).

Mean cholesterol values were elevated for the 500, 1000, 2000, 4000, and 8000 ppm females throughout the study (Table 4). Mean SGOT values were slightly decreased for all treated female groups at 18 and 24 months when compared to controls.

Table 4. Mean Chlosterol Values For Female Rats (10/dose) for Command.

Dose (ppm)	0	20	100	500	1000	2000	4000*	8000*
Baseline	65.2±12.6	-	-	-	-	-	-	-
3 mo	66.7±18.4	70.0±20.1	77.1±15.2	73.9±18.3	14.5±33.5	83.3±17.3	95.7±10.7	118.0±20.2
6 mo	98.3±21.6	88.7±17.4	108.9±35.6	122.1±35.9	103.2±35.9	132.5±38.7	-	-
12 mo	97.4±21.6	100.5±27.4	102.7±22.9	83.1±24.3	125.4±38.5	122.2±22.4	-	-
18 mo	103.6±40.6	109.6±31.3	121.0±25.3	144.3±87.6	118.3±32.2	133.8±32.2	-	-
24 mo	131.3±44.1	187.2±1.26	138.2±51.3	203.3±113.7	191.1±88.4	191.1±88.4	-	-

* Doses terminated at 3-month sacrifice.

Urinalysis: Although slight variations were observed throughout the study, treatment groups were similar to control groups.

Organ weights: At 24 months, the liver to body weight ratio and the liver to brain weight ratio, was increased for all the treated female groups when compared to controls (Table 5). Some variability was observed in kidney and liver organ to body weight ratio and organ to brain weight ratio in other male and female groups, however, no distinct trends were evident.

Table 5. Liver Weight Data For Female Rats Fed Command for 24 Months.

Dose (ppm)	0	20	100	500	1000	2000
Body Wt(g)	461.6995 ±99.7113	434.5519 ±104.7798	470.5619 ±111.6021	476.3248 ±109.3774	456.5895 ±91.6244	425.6657 ±117.5312
Liver/Body Wt(g/100g)	2.4789 ±.03601	2.9710 ±0.6465	2.6749 ±0.4606	2.8264 ±0.6515	2.9767 ±0.4662	3.1703 ±0.514
Liver/Brain Wt(g/g)	5.3524 ±1.1617	5.9020 ±1.3905	5.9006 ±1.2649	6.2231 ±1.3072	6.3883 ±1.3851	6.3342 +2.0631

Pathology: Hitopathological examination of the individual animal data demonstrated a non-statistical increase in pheocromocytomas and hepatocellular adenomas in male treatment groups between 18 and 24 months when compared to concurrent controls (Table 6). As requested, the Petitioner has submitted historical control data from Toxigenics for letter from Cuirle [FMC] to Taylor [EPA], dated December 21, 1984; letter attached to this review).

The Branch's Peer Review Group (Dr. Ted Farber, Mr. William Burnam, Dr. Reto Engler, Mr. Bert Litt, Dr. Robert Zendzian) met on December 21, 1984 to discuss the biological relevance of these tumors. The group unaminiously agreed that no dose response relationship was observed, that a more than adequate dose spread was employed, that the historical control data submitted indicate a high degree of variability in the incidence of these types of tumors, and that the low incidence observed in the concurrent controls was within the range of variability. Therefore, based on these facts, the incidence of pheochromocytoma and hepatocellular adenoma observed in this study do not represent an oncogenic potential.

Table 6. Histopathology for Selected Lesions In Males

Dose (ppm)	0	20	100**	500	1000**	2000
Adrenals - Pheocromocytoma						
0-3 months	0/40	0/40	0/20	0/40	0/20	0/40
6 months	0/10	0/10	0/10	0/10	0/10	0/10
12 months	0/10	0/10	0/10	0/10	0/10	0/10
18 months	0/23	1/15	0/16	1/17	0/18	0/20
24 months	0/37	3/45	4/44	3/43	5/42	3/40
	0/120	4/120	4/100	4/120	5/100	3/120
Hepatocellular - Adenoma						
0-3 month	0/40	0/40	0/20	0/40	0/20	0/40
6 months	0/10	0/10	0/10	0/10	0/10	0/10
12 months	0/10	0/10	0/10	0/10	0/10	0/10
18 months	0/23	1/15	0/16	1/17	0/18	1/20
24 months	1/37	4/45	1/44*	6/43	0/42	2/40
	1/120	5/120	1/100	7/120	0/100	3/120

* This group also had one (1) hepatocellular carcinoma

** These dose groups were not histologically examined at the three month sacrifice.

NOTE: The denominator is a combination of scheduled sacrificed animals and those animals which died subsequent to the prior sacrifice.

FMC Corporation

Agricultural Chemical Group
2000 Market Street
Philadelphia, Pennsylvania 19103
215 299 6000

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FMC

December 6, 1984

Mr. Robert J. Taylor (PM-25)
U.S. Environmental Protection Agency
Office of Pesticide Programs
Registration Division (TS-767-C)
Crystal Mall, Building 2
1921 Jefferson Davis Highway
Arlington, VA 22202

Dear Mr. Taylor:

Subject: Command[R] Herbicide
Pesticide Petition No. 4F3128
Rat Study
Your Letter Dated 11/20/84

We have received your request for historical control data on the incidence of pheochromocytoma, hepatocellular adenoma, hepatocellular carcinoma and hepatocellular megalocytosis in the rat two-year feeding studies conducted at ToxiGenics, Inc. We contacted ToxiGenics concerning the availability of such data. In this regard, please find enclosed the following historical control data:

	ToxiGenics Study 410-0866 (Ethion)	ToxiGenics (Unnamed Study)
Pheochromocytoma	X	X
Hepatocellular Megalocytosis	X	-
Hepatocellular Carcinomas	X	-
Neoplastic Nodules (Hepatocellular Adenomas)	X	-

Please note that the term "neoplastic nodule" is used for the lesion described as an adenoma. Also, concerning ToxiGenics "unnamed study", this study was not commmissioned by FMC Corporation. It was explained to us that this is a recent study and the liver slides have not been read yet. Hence, only the requested data concerning pheochromocytoma is available at this time.

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To our knowledge, the aforesaid studies, in addition to the rat two-year feeding study using Command^{R} Herbicide (FMC 57020), presently comprise the historical control data base for chronic feeding/oncogenicity studies performed by Toxi-Genics using Sprague Dawley rats. We trust that the enclosed information is sufficient for the completion of the rat chronic feeding review.

If you have any questions concerning this submission, please call. My telephone number is 215/299-6999.

Sincerely,

Eunice M. Cuirle

Eunice M. Cuirle
Registration Specialist

Enclosures

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EXPERIMENTAL PATHOLOGY LABORATORIES, INC.
1800 EAST PERSHING ROAD, DECATUR, ILLINOIS 62526 (217) 875-3930

November 30, 1984

Mike Norvell, Ph. D.
Manager, Toxicology
Agricultural Chemicals
FMC Corporation
Route 1
Plainsboro Road
Princeton, NJ 08540

Dear Dr. Norvell:

The following is the preliminary incidence data I have found for the incidence of select liver lesions in ToxiGenics Study 410-0866 (Ethion) from 18 through 24 months.

	Neoplastic Nodules	Hepatocellular Carcinoma	Megalocytosis
Females			
Final Sac	3/28	----	3/28
Found dead	----	----	1/13
Males			
Final Sac	1/30	2/30	4/30
Found dead	1/15	----	----

The criteria I use for diagnosis of "neoplastic nodules" are essentially the same most pathologists use for "hepatocellular adenoma".

Sincerely,

W. O. Iverson, D.V.M.

W.O. Iverson, D.V.M.

WOI/jcs

cc: ToxiGenics P.A., LDM

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EPL
EXPERIMENTAL PATHOLOGY LABORATORIES, INC.
1800 EAST PERSHING ROAD, DECATUR, ILLINOIS 62526 (217) 875-3930

November 21, 1984

Mike Norvell, Ph.D.
Manager, Toxicology
Agricultural Chemicals
FMC Corporation
Route 1
Plainsboro Road
Princeton, N.J. 08540

Dear Dr. Norvell:

The following is the historical incidence data I have found for pheochromocytomas in male untreated control Sprague-Dawley rats.

A. From Hazelton Laboratories, about 1979-1984, cumulative data from the 24 month sacrifice from 8 studies.

Malignant pheochromocytomas 2/303 (0.7%)
Benign pheochromocytomas 47/303 (16%)
Range 0-26%

B. ToxiGenics study 410-0866 (Ethion)

18 month sac and mortalities 12-18 months 0/15
24 month sac and mortalities 18-24 months
Benign pheochromocytomas 8/45 (18%)
Malignant pheochromocytomas 0/45

C. Other unnamed study at ToxiGenics.
Vehicle controls which received distilled water by gavage.

12 month sac and 0-12 month mortalities 0/9
24 month sac, benign pheochromocytomas 3/13 (23%)

This is all the information I have available on the incidence of pheochromocytomas in this strain of rat.

Sincerely,

W.O. Iverson, D.V.M.

W.O. Iverson, D.V.M.

WOI/jcs

cc: ToxiGenics Project Administration

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Command toxicology review

Page _____ is not included in this copy.

Pages 20 through 23 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

✓ FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

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FF

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY 004173
WASHINGTON, D.C. 20460

NOV 20 1984

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

FMC Corporation
Agricultural Chemical Group
2000 Market Street
Philadelphia, PA 19103

Attention: Eunice M. Cuirle

Gentlemen:

Subject: Command Herbicide
Pesticide Petition No. 4F3128
Rat Studies

In order to complete the review of the chronic feeding/oncogenicity study in rats (Toxigenics, Inc. Study 410-0816, FMC Study A81-650, dated July 10, 1984), the Agency is requesting historical control data for the same strain of rats, conducted at the same contracting lab used in this study from 1979 through 1984, with a summarization (study by study) of the incidence of pheochromocytoma, hepatocellular ademona, hepatocellular carcinoma, and hepatocellular magalocytosis.

These data should be submitted as soon as possible to insure a complete review without a delay in the schedule.

Sincerely yours,

Robert J. Taylor
Product Manager (25)
Fungicide-Herbicide Branch
Registration Division (TS-767C)

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C04173

COMPOUND: Command (FMC 57020)

FORMULATION: Technical (91.4% Purity)
(Lot No. Ref. E1756-146 and assigned HLA Sample No. 989996)

CITATION: Final Report. 1-year Chronic Oral Toxicity Study in Dogs according to EPA Guidelines. (FMC Study No. A82-759; HRI Study No. 6124-101). June 22, 1984. Unpublished report by Hazleton Laboratories America, Inc. for FMC Corporation.

Accession No.: 072828

Reviewed by: Carolyn Gregorio, Toxicologist
Toxicology Branch/HED (TS-769)

12/12/84
12-12-84

CORE CLASSIFICATION: Minimum

TOXICITY CATEGORY: Not Applicable

CONCLUSION: An increase in cholesterol and liver weights (absolute and relative to body weight) were observed in the 2500 and 7500/5000 ppm males and females when compared to concurrent controls throughout the study.

NOEL = 500 ppm
LEL = 2500 ppm

Homogenicity of Command in Mixed Diets: The data submitted (Petitioner's Table 50) shows that two diet mixes were performed. On the first date (December 15, 1982) the assays for 100 ppm and 7500 ppm groups "were too low [25-50% lower than required] and variable. Therefore the homogenicity analyses were repeated with the revised analytical procedure." The next assay (February 22, 1983), which is the only other recorded assay does show reasonable improvement.

Stability of Command In Mixed Diets: The data provided (Petitioner's Tables 51 and 52) indicate that the diets were stable for 1 month when kept frozen.

Materials and Methods: Beagle dogs (4-6 months old) weighing 6.0 to 9.0 kg at study initiation were received from Hazleton Research Animals. After a 2-week acclimation period, six animals/sex were assigned at random to various groups. The compound was administered in the diet at concentrations of 0, 100, 500, 2,500, or 7,500/5,000 ppm (at day 8, the high dose groups were reduced from 7,500 ppm to 5,000 ppm) for 1 year.

"Diets were prepared fresh every week. Corn oil was mixed at a level of 2% by weight" with the test material.

The eight following parameters were recovered throughout the study:

1. Clinical observations and modality.

2. Body weight and food consumption.

3. Ophthalmic examination.

4. Hematology (erythrocyte count, hemocrit, hemoglobin, leukocyte, count (total), leukocyte count differential (neuropil, lymphocyte, monocyte, eosinophil, basophil, bands segments), platelet count, nucleated red blood cells).

5. Blood chemistry (albumin, blood urea nitrogen, calcium, chlorine, creatine phosphokinase, creatinine, gamma glutamyl transpeptisase, glucose, inorganic phosphorous, potassium, SGOT, SGPT, sodium, total bilirubin, total chloresterol, total protein).

6. Urinalysis (physical appearance, pH, specific gravity, bilirubin, blood, glucose, ketones, protein, urobilinogen, microscopic examination of sediment).

7. Organ weights (adrenals, brain, gonads, heart, kidneys, liver thyroid with parathyroid).

8. Pathology/histopathology (adrenals, aorta, brain, duodenum, ileum, jejunum, cecum, colon, rectum, esophagus, eyes, femur with bone marrow, gall bladder, gonads, heart, kidneys, liver, lungs, mesenteric and prescapular lymph nodes, pancreas, pituitary, prostate, salivary gland, sciatic nerve, skeletal muscle, spinal cord, spleen, stomach, thymus, thyroid, trachea, urinary bladder; all gross lesions).

Results: Clinical Observations - Although the Petitioner's submitted text indicates that "during the first weeek on test, the 7,500 ppm dose group defecated infrequently, and feces when present, were usually mucoid and/or bloody...the dose level was reduced to 5,000 ppm." None of the dogs on test died during the study. Two dogs/sex/dose were sacrificed at 90 days (citation).

Body Weight and Food Consumption: Body weight gains were decreased (10-20%) for the high dose males (7,500/5,000 ppm) throughout the study when compared to concurrent control animals. Food consumption for this group was similar or higher throughout the study, except for Week 1 when dose levels were 7,500 ppm and subsequently dropped to 5,000 ppm.

Body weight and food consumption were similar for all female groups throughout the study.

Based on the data provided (Table 9 and Table 10). The following is the average theoretical intake of Command over the 52-week period:

Dose (ppm)	0	100	500	2,500	7,500/5,000
Male (mg/kg/day)	0	2.8	14.0	67.5	140.5
Female (mg/kg/day)	0	3.0	14.9	76.3	151.4

Ophthalmic Examination: Eye examination was similar for treated and control animals. Eye lesions noted at the beginning of the study showed no deterioration over the 52 weeks.

Hematology: Normal biological variations were observed in all examined hematology parameters except for platelet counts. Platelet counts were elevated for males (500, 2,500, 7,500/5,000 ppm) and females (2,500 and 7,500/7,500 ppm) dose groups when compared to control animals (Table 1).

Dose (ppm)	0	100	500	2,500	7,500/5,000
Males					
Month 0**	353	393	468	392	385 (9)
1**	297	301	361 (17)	346 (14)	314 (6)
3**	488	539	661 (26)	590 (17)	651 (25)
6***	331	340	409 (19)	361 (-)	390 (15)
12	286	242	400 (28)	349 (18)	402 (29)
Females					
Month 0**	437	412	420	398	416
1**	297	358	347	359 (17)	420 (29)
3**	574	563	577	630 (9)	826 (31)
6***	356	381	386	438 (19)	562 (37)
12***	378	370	392	458 (17)	542 (30)

( ) = Percent increase between means of treatment and control groups.
* = Dose level changed from 7,500 to 5,000 ppm after 1 week.
** = Six animals/sex/dose mean.
*** = Four animals/sex/dose.

In addition, red blood cell counts, hemoglobin and hematocrit. Values were slightly decreased at 1, 3, and 6 months for the high dose males and females. However, these values were similar to control values at termination of the study.

Blood chemistry: Normal biological variations were observed in all the blood chemistry parameters examined, except for cholesterol. Cholesterol counts were elevated for the 2,500 and 7,500/5,000 dose males and females throughout the study (Table 2).

Table 2. Mean Cholesterol (mg/dl) for Dogs Fed Command over 1 Year

Dose (ppm)	0	100	500	2,500	7,500/5,000
Males					
Month 0**	136.9	159.4	144.5	142.4	151.1
1**	122.1	133.2	120.6	155.1 (21.2)	168.2 (27.4)
3**	123.4	147.3	130.5	152.2 (18.9)	168.8 (26.9)
6***	128.2	127.5	111.4	153.1 (16.3)	161.1 (20.4)
12***	130.8	135.6	130.3	157.2 (16.7)	191.7 (31.8)
Females					
Month 0**	116.8	117.9	137.1	119.3	130.6
1**	105.6	110.2	119.6 (11.6)	123.0 (14.1)	164.7 (35.8)
3**	108.6	114.5	116.5 (6.8)	136.6 (20.5)	149.4 (27.3)
6***	109.0	116.0	127.7 (14.6)	124.7 (12.6)	143.7 (24.1)
12***	144.9	143.6	134.2 (-)	161.7 (10.4)	165.9 (12.6)

( ) = Percent increase between means of treatment and control groups.
* = Dose level changed from 7,500 to 5,000 ppm after 1 week on study.
** = Six animals/sex/dose mean.
*** = Four animals/sex/dose mean.

It should be noted that the values for the gamma glutamyl transpeptidase (GGT) were extremely variable and in some cases at the level of detection. These readings made an assessment of these values impossible.

Urinalysis: Normal biological variations were observed in all the urinalysis parameters examined, except for the amount of protein (mg/dl) found in the treated females, when compared to concurrent females (Table 3).

Table 3. Mean Protein (mg/dl) in Urinalysis of Females

Dose (ppm)	0	100	500	2,500	7,500/5,000
Month 0**	36.3	23.3	20.0	15.0	30.0
1**	13.3	23.3	23.3	16.7	13.3
3**	31.6	11.7	10.0	8.3	10.0
6**	25.0	15.0	20.0	10.0	30.0
12**	42.5	535.0	535.0	602.5	1,077.5

* Six females/sex/dose.
** Four females/sex/dose.

Organ Weights: An increase in mean absolute liver weight and mean relative liver to body weight ratio was observed in all treatment groups (Table 4). Other organs examined (brain, ovary) showed some variation but are considered not of significant interest.

Gross and Microscopic Pathology: No noteworthy changes were observed in any of the dogs.

Table 4. Mean Liver Weights for Dogs Fed Command

Dose (ppm)	0	100	500	2,500	7,500/5,000
Male					
3 month					
o body weight (gm)	10,050	10,550	8,800	10,100	10,400
o absolute weight (gm)	262.9500	282.2905	222.3660	313.8795	360.4640
o relative weight (%)	2.6166	2.6736	2.5220	3.1145	3.4694
12 month					
o body weight (gm)	12,050	11,850	13,025	12,125	9,975
o absolute weight (gm)	284.6333	296.3442	310.5695	320.9835	342.6385
o relative weight (%)	2.3601	2.4978	2.4294	2.6645	3.4357
Female					
3 month					
o body weight (gm)	8,750	8,950	8,900	9,200	9,250
o absolute weight (gm)	219.2870	253.2680	249.4220	299.4220	314.8815
o relative weight (%)	2.5113	2.8559	2.8049	3.2585	3.4032
12 month					
o body weight (gm)	9,775	11,450	10,675	10,550	9,625
o absolute weight (gm)	266.6715	294.4625	258.6873	269.9290	271.5786
o relative weight (%)	2.3317	2.6096	2.4402	2.5745	2.8278

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

004173

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

DATE: December 26,1984

SUBJECT: Toxicology Branch's Peer Review Group Pathology Discussion Of 2-Year Feeding/ Onco Study In Rats and 2-Year Feeding/Onco In Mice Fed COMMAND.

TO: The COMMAND Data File

FROM: Carolyn Gregorio, Toxicologist CAG 12-26-84
Toxicology Branch/HED (TS-769)

THRU: Robert P. Zendzian, Ph.D. 12/26/84
Acting Section Head/ Section III
Toxicology Branch/HED (TS-769)

Chemical: COMMAND, FMC 57020

Caswell No.: 463D

Petitioner: FMC Corporation

The Toxicology Branch's Peer Review Group (Dr. Ted Farber, Mr. William Burnam, Dr. Reto Engler, Dr. Robert Zendzian, Mr. Bert Litt) met on December 21, 1984 to disuss the histopathology findings in the chronic feeding/onco studies submitted in support of the Petitioner's COMMAND petition requests.

1.) 2-Year Feeding/Onco - Sprague-Dawley Rat

Histopathology examination of individual animal data of the 2-year feeding/ onco study in rats (FMC Study No. A81-650; Toxigenics Study No. 410-0816; dated July 10, 1984), demonstrated a non-statistical increase in pheochromocytomas and hepatocellular adenomas in male treatment groups

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between 18 and 24 months when compared to concurrent controls. The study incidence for benign pheochromocytoma was 0/60, 4/60, 0/60, 4/60, 5/60, and 4/60 for the 0, 20, 100, 500, 1000, and 2000 ppm dose groups, respectively. The study incidence for hepatocellular adenoma was 1/60, 5/60, 1/60, 7/60, 0/60, and 3/60 for the 0, 20, 100, 500, 1000, and 2000 ppm dose groups, respectively. A slight elevation in cholesterol, liver to body weight ratio, and liver to brain weight ratio was observed in the 500, 1000, and 2000 ppm females only; no other indications of possible treatment related effects were observed.

The Peer Group unaminiously agreed that no oncogenic potential was demonstrated in this study based on the following facts:

a.) no dose response relationship was observed,
b.) a more than adequate dose spread was employed,
c.) the historical control data submitted by the Petitioner indicate a high degree of variability in the incidence of these types of tumors, and
d.) the low incidence in the concurrent controls of this study was within the range of variability.

2.) 2 Year Feeding/Onco - Charles-River CD-1 Mice

Histopathology examination of individual animal liver data in the 2-year feeding/onco study in mice (FMC Study No. A81-651; Toxigenics Study No. 410-0817) demonstrated a non-statistical increase in hepatocellular adenoma and hepatocellular carcinoma in males. In addition, hepatocellular cytomegaly was observed more frequently in treatment males.

Liver Pathology In Male Mice Fed COMMAND For 2 Years

DOSE PPM	0	20	100	500	1000	2000
Adenoma	14/67	9/68	9/69	9/70	9/69	8/69
Carcinoma	3/67	3/68	9/69	7/70	10/69	3/69
	17/67	12/68	18/69	16/70	19/69	11/69
Cytomegaly	1/96	3/91	3/89	2/100	5/89	12/99

The Branch Peer Review Group unaminiously agreed that no oncogenic potential was demonstrated with regard to the liver pathology data presented based on the following:

generally represent the histogenetic development of tumors and adding them together minimizes the effect of pathologists using different terminology).

In addition, the Peer Review Group agreed that the obsevation of the hepatocellular cytomegaly in this study was an indication of liver toxicity.

004173

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

DATE: December 20, 1984

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Discussion Of COMMAND Oncogenicity Data With Lab Audit Personnel

TO: Ted Farber, Ph.D.
Branch Chief,
Toxicology Branch/HED (TS-767)

FROM: Carolyn Gregorio, Toxicologist CAG 12-20-84
Toxicology Branch/HED (TS-767)

12/26/84

THRU: Robert P. Zendzian, Ph.D.
Acting Section Head/ Section III
Toxicology Branch/HED (TS-767)

Chemical: COMMAND; FMC 57020

Caswell No.: 463D

Petitioner: FMC Corporation

As requested, Dr. Zendzian and I discussed the preliminary review results of the two COMMAND oncogenicity studies submitted by the Petitioner in support of their registration requests with Dr. Adrian Gross (Chairman For Laboratory Inspection And Data Audit Program).

Dr. Gross has conducted a data audit/laboratory inspection for Toxigenics, which was the contracting lab used for the COMMAND oncogenicity studies. The lab audit was conducted in response to the receipt of a letter to the Agency in which unspecified improprieties were alleged. Although Dr. Gross did not have a copy of the written report, he told us that the audit did not show any problems with regard to the COMMAND oncogenicity studies.

In addition, Dr. Gross indicated that he had looked at the oncogenicity portions of the two COMMAND long term studies. In our discussion of the data, we were in agreement that data do not suggest an oncogenic potential, but do

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demonstrate a non specific liver toxicity pattern. This pattern was evidenced in both studies by the trends established in the incidence of hepatocellular megalocytosis and increased absolute and relative liver weights (Dr. Gross's notes on these findings are appended to this note).

Hep. Cytomeg. mouse - male 004173

	N. A.			Adj.	
0	1/81	1.23 %	0	1/36	2.7778 %
10	0/79	0.00 %	10	0/79	0.0000 %
100	3/80	3.75 %	100	2.3779 / 26.4854	8.9783
500	4/80	5.00 %	500	3.2186 / 35.1317	9.1615
1000	4/80	5.00 %	1000	2.9629 / 35.0079	8.4645
2000	18/81	22.22 %	2000	16.5767 / 47.6314	34.8021

N. A.	Adj.
9.720 -5	1.556 -4
1.473 -5	2.311 -5
40.082	38.861
0.000,000,000,125	0.000,000,000,228
5.297	4.394
4	4
0.258	0.355

Mean Y = 6.2370 % 26.1361 / 259.2524 = 10.0813 %

Mean X = 606.195726 586.536865

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...se – male Hep. Cytomegaly . 004173

	0	T_I	T_{II}	T_{III}	T_{IV}	T_V
0-6 mos.	0/4 ✓	0/1	0/11 ✓	0/0 ✓	0/1 ✓	0/2 ✓
-12 mos.	0/2 ✓	0/7	0/8 ✓	0/4 ✓	0/4 ✓	0/4 ✓
-18 mos	0/9 ✓	0/10	2/10 ✓	2/9 ✓	1/10 ✓	2/9 ✓
-24 mo	1/16 ✓	0/10	0/12 ✓	0/14 ✓	0/12 ✓	3/14 ✓
4 mos. sacr.	0/20 ✓	0/21	1/19	1/23 ✓	1/23 ✓	3/22
8 mos. sacr.	0/10 ✓	0/10	0/10 ✓	0/10 ✓	0/10 ✓	2/10 ✓
2 mos. sacr.	0/10 ✓	0/10	0/10 ✓	1/10 ✓	0/10 ✓	3/10 ✓
6 mos. sacr.	0/10 ✓	0/10	0/10 ✓	0/10 ✓	2/10 ✓	5/10 ✓
	1/81	0/79	3/80	4/80	4/80	18/81

0	1/81	9.720 -5
20	0/79	1.473 -5
00	3/80	40.082
00	4/80	0.000,000,000,122
00	4/80	5.297
00	18/81	4
		0.258

try also after 12 mos. only

or 1/81 / 3/80 N.S. / 4/161

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C.

U.C. Adj. 1/36 = 2.7778 % 36 E.N.

TI 0/79 = 0.0000 % 79 E.N.

T? 2.377945/26.485391 = 8.9783 % 26.48539

(4, 10, 2, 10, 9, 10) 1/36

T_2

80					
79	1				
69	10				
61	8				
51	10	2/10	.960784	0.039216	51
49					
38	10				
19	12	.110	.01A717	.A89703	26.485391

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(without masses) U.T. [illegible] g der [illegible].
Book 1 of 20 Table 26 p. 5.

004113

Ratio G/100 G	20	100	500	1,000	7,000	Total
2	16	13	17	16	15	89
36	79.0112	64.4124	85.9214	84.4128	86.495	457.7164
980)	395.98943/2	322.7898054	445.0118465	456.192752)	506.1057065	274... 88272
33	4.9382	4.9548	5.0542	5.2758	5.7610	5.14288081
681	4.8769	4.9117	5.0860	5.3938	5.7395	
27	~~5.1116~~	~~5.1865~~	~~5.2507~~	~~5.5786~~	~~6.0245~~	~~0.8149~~
18	0.6227	0.5507	0.8196	0.8504	0.7685	0.8119
				S_Y : 58.01199899		0.65922
64	5.81632935	3.63924588	10.7490656	10.847024	8.2682915	
251	390.1731078	319.1505595	434.2639399	445.3450503	497.836815	

6120 — ΣXY : 308224.954 — $S_{y.x}$: 49.4593186

386400 — S_{XY} = 196054879 — $s^2_{y.x}$: 0.568612858

0.5617978 — b = 0.000435707 — $s^2_{b_{y.x}}$: 0.000000011

4999271.9 — S_3 : = 8.542579726

: 0.0761/1819 — S_2 : 0.184687274 — $s_{b_{y.x}}$: 0.00011241

0.5937 90739 — S_1 : 49.28463133 — t = 3.87604 4231

0.07775/728 — 58.01199833 — $p(t_{87})$: 0.000,103

$(4, 83)$ = 0.988,881

: 0.0026638 33

$)$: 0.999,999,114

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004175

	20	100	500	1000	2000	Total
	16	13	17	16	15	89
2	28.1296	22.6534	30.7802	30.0304	30.2025	161.8257
076	50.26479616	~~39.47651188~~ 40.41798	57.02021748	57.78332416	62.60502551	302.2418552
1	1.7581	1.7426	1.8106	1.8769	2.0135	1.818266292
;	1.7285	1.7403	1.7991	1.8726	2.0195	

4	0.8101464	0.94147212	1.28958736	1.4192664	1.79229176	Sy = 7.99963968
2	49.45464976	39.47651188	55.73063012	56.36405776	60.81273375	

ΣXY 108653.472

17978 S_{XY} ~~107506.9427~~ 5512.3677

271.9 b : ~~0.00238908~~ 0.00014 6944

S_3 0.97164 6979

S_2 0.05545 8621 s_2^2 = 0.01386 4655

S_1 6.97253 4080 s_1^2 = 0.08400 6435

7.99963968

$F_{(4,43)}$ = 0.165042777

$p(F)$ = 0.956

$S_{y.x}$ = 7.027992701

$s^2_{y.x}$ = 0.80781525

$s^2_{b_{y.x}}$ = 0.000000002

$s_{b_{y.x}}$ = 0.000042369

t = 3.468152835

$p(t)$ = 0.000,408,41

0.0024610 75

= 0.999,999,244

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(constant masses) 4% males 1... ... (G/C) Ratio Book 1 of 20 Table 26 p.?

004173

20	100	500	1,000	2,000	Total
16	13	17	16	15	89
48.2656	39.8853	54.2776	54.7856	54.6075	288.8716
149.177492	125.5239639	178.2276975	193.8763823	204.7245187	971.1544371
3.0166	3.0681	3.1928	3.4241	3.6405	3.245748311
3.0566	3.0814	3.2053	3.3602	3.6700	
3.579413 75	3.157875	4.9301616	6.28495931	5.925915 04	S_y = 33.54992820
45.5980089	122.3720889	173.2975213	187.5913729	198.798603	

ΣYX = 196093.242

S_{XY} = ~~194096.5971~~ 13971.4761

b = 0.000,309,424

S_3 = 4.319516259

S_2 = 0.12544554 1 r_2^2 = 0.031361555

S_1 = 29.10496629 r_1^2 = 0.3506622 45

33.54992809 $F_{(4,83)}$ = 0.0894...

$S_{y.x}$ = 29.23041183   p(F) = 0.98...

$r^2_{y.x}$ = 0.335981745

$s^2_{b_{y.x}}$ = 0.000,000,007

$s_{b_{y.x}}$ = 0.000,086,408

$t_{(87)}$ = 3.5855 8 2470

p(t) = 0.000,277,25

'4

'1.9

2533127

.999,999,199

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... Statistical Study ... females

Rel. Liver (to Brain Wt) Wt males, Final Sac Table 29 p

004173

0	20	100	500	1000	2000	To
22	25	27	21	22	30	1
117.7528	147.55	159.3162	155.5775	140.5426	190.0260	910.
58.6005715	917.243866	981.6604419	1009.184865	938.1168336	1327.09756	583 .90
5.3524	5.9020	5.9006	6.2231	6.3883	6.3342	6.0315
5.8193	5.8259	5.8521	5.9833	-6.1473	6.4753	
8.34048469	46.403766	41.59927226	41.01052416	40.28854221	123.7350667	
30.2600868	870.8401	940.061196	968.1743404	897.8282914	1203.662689	

7700

18530000

47.0198675

5316158.94

$S_y = 338.5727628$

ΣXY 617255.97

S_{xy} 27982.8556

$b = 0.00032799$

$S_3 = 9.178099637$

$S_2 = 8.317005363$ $s_2^2 = 2.079251$

$S_1 = 321.0776561$ $s_1^2 = 2.1991620$

338.5727611

$F_{(4, 175)} = 0.945474$

$p(F) = 0.739,6$

$r_y^2 = 0.0609904$

$(\chi^2_y) = 0.999,544$

$S_{y.x} = 329.3946615$

$s^2_{y.x} = 2.210702426$

$s^2_{b\,y.x} = 0.000,000,026$

$s_{b\,y.x} = 0.000160972$

$t = 2.037563912$

$p(t_{149}) = 0.021682$

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Rel. Liver (to B.W.) wt. [illegible]

004173

0	20	100	500	1000	2000	Total
22	25	27	25	22	30	151
.5358	74.275	72.2223	70.66	65.4874	95.109	432.2895
.9189064	230.702119	198.703917	209.900278	199.5005348	310.0243675	12867.42598
.4789	2.9710	2.6749	2.8264	2.9767	3.1703	2.862844371
.7108	2.7155	2.7343	2.8283	2.9458	3.1807	
231231	10.031094	5.51596136	10.186854	4.56419124	8.50030484	
1.1887976	220.671025	193.1874303	199.7134Z4	194.9363436	301.5240627	

$S_y = 49.16503601$

97700
148530000
647.0198675
~~97052.95016~~
~~3791.829286~~
85316158.94

$\Sigma XY = 299743$

S_{xy} 20043.235

$b =$ ~~0.2065184?1~~ 0.000234929

$S_{y.x}$ 44.45629965

$s^2_{y.x}$ 0.29436442?

$s^2_{b.y.x}$ 0.000 000 003

$s_{by.x}$ 0.00005913?

$t = 3.972634865$

$p(t_{149}) = 0.000,055,2$

$S_3 = 4.708736003$

$S_2 = 2.934781997$ $s_2^2 = 0.733695499$

$S_1 = 41.52151765$ $s_1^2 = 0.286355294$

49.16503565

$F = 2.562185908$

$p(F_{4,145}) = 0.040,929$

$\chi^2_y = 0.0455\,27958$

$p(\chi^2_y) = 0.999,745$

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Abs. liver wt. Fem. Final sacr. Table 29 p. 7

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0	20	100	500	1000	Tokuo [illegible] 2006	Total
22	25	27	25	22	30	151
278.6022	312.8	337.0332	326.8525	295.9044	401.985	1920.1773
922.20166	4135.39157 ~~3913.7536~~	4302.49301	4459.69237	4165.32454	5962.53033	25947.63344
11.3001	12.5728	12.3716	13.0741	13.4502	13.3995	12.71670596
2.2571	12.2713	12.3281	12.6120	12.9670	13.6769	S_y = 1529.87938
12.9719436	221.637917	169.9678822	186.3901018	185.357183	576.1323234	1452.451351
309.22971 ~~3.8119736~~	3913.7536	4132.525737	4273.302272	3979.973361	5386.398007	

x 97700
y^2 178530000
– 647.0198675
85316158.94

= 0.12015808

) = 0.998,266

ΣXY = 1302959.97
S_{YY} = 60567.108
b = 0.00070971[illegible]

$S_{Y \cdot Y}$ 1486.881973
$s^2_{Y \cdot Y}$ 9.97907364
$s^2_{b_{Y \cdot Y}}$ 0.000000117
$s_{b_{YY}}$ 0.000342003
t = 2.07575492
$p(t_{149})$ = 0.019818

S_3 42.99741827
S_2 34.43062173 s_2^2 = 8.607[illegible]
S_1 1452.451351 s_1^2 = 10.01690[illegible]
1529.879391 F = 0.859312[illegible]
$p(F_{4,145})$ = 0.490077

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