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

APR - 6 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA ID # 067501. Piperonyl butoxide: Review of a series 83-1(b) chronic feeding study in dogs.

TOX CHEM No.: 670
PC No.: 067501
Barcode No.: D195294
Submission No.: S448786

FROM: John Doherty *John Doherty 3/24/95*
Section IV, Toxicology Branch I
Health Effects Division (7509C)

TO: Jay Ellenberger/Alan Dixon
Product Manager #50
Special Review and Reregistration Division (7505C)

THROUGH: Marion Copley, DVM, Section Head *Marion Copley 4/4/94*
Section IV, Toxicology Branch I
Health Effects Division (7509C)

I. CONCLUSION

The series 83-1(b) chronic feeding study in dogs was reviewed and determined to be CORE GUIDELINE. No additional series 83-1(b) study data are required at this time. The study supports a NOEL and LEL of 100 and 600 ppm based on decreased body weight and trends for increased liver weight and alkaline phosphatase. A copy of the DER is attached.

II. Action Requested

The McKenna & Cuneo Law Office on behalf of the Piperonyl Butoxide Task Force II has submitted a series 83-1(b) chronic feeding study with dogs in support of the reregistration requirements for piperonyl butoxide. The study is further identified in part III below. The study was reviewed and determined to be CORE GUIDELINE and a copy of the DER is attached.

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III. Executive Summaries of Studies Reviewed.

Series 83-1b. Chronic Feeding - dogs. International Research and Development Corporation. Study No.: 542-005, September 9, 1993.

Four groups of 4/sex beagle dogs were dosed with 0 (controls), 100, 600 or 2000 ppm diets containing piperonyl butoxide (PBO, 90.78% purity but as 100% a.i.) for one year. These doses correspond to 2.9, 15.5 or 52.8 mg/kg/day PBO in males and 2.7, 16.3 or 71.0 mg/kg/day PBO in females. The dogs were assessed daily for reactions and weekly and later biweekly for body weight and food consumption. Clinical hematology, chemistry and urinalysis were assessed at 6 months and termination and organ weights and pathology were assessed at termination.

Reactions to treatment were noted at 600 ppm and above. At 600 ppm there was decreased body weight gain with males gaining only 16% in the mid and 3% in the high dose groups while controls gained 24.8% and females in the mid dose gaining only 19.8% and high dose showing a decrease in weight gain of 2% whereas the controls gained 21.8%. Decreases in food consumption paralleled the body weight changes in males but not females. At 2000 ppm, serum alkaline phosphatase was elevated in males (340% at 6 months and >500% at 1 year) and females (368% at 6 months and >600% at 1 year). Mid dose group males were elevated about 60% at each interval but not significantly. Terminal high dose group liver weight was also increased in males (22% absolute and 52% relative) and females (36% absolute and 86% relative). Elevations in female liver weight (12% absolute and 13% relative) were also apparent. The high dose males (3/4) and females (all 4) had hepatocellular hypertrophy, a condition not reported in any other test groups. The LEL is 600 ppm based on decreases in body weight gain in both sexes with trends for increased alkaline phosphatase and liver weight noted. The NOEL is at 100 ppm.

Classification: CORE-GUIDELINE. The study satisfies the requirement for a series 83-1(b) chronic feeding study in non-rodents. No additional series 83-1(b) study data are required at this time.

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83-1 (dog). Piperonyl butoxide/1993
Reviewed by: John Doherty, Ph.D. *John Doherty* 4/4/94
Section IV, Tox. Branch (7509C)
Secondary reviewer: Marion Copley, DVM *Marion Copley* 4/9/94
Section IV, Tox. Branch (7509C) 010885

DATA EVALUATION REPORT

STUDY TYPE: 83-1. Chronic dosing - dog

TOX. CHEM. NO.: 670
PC No.: 067501

MRID NO.: 429260-02 (definitive study)
429260-01 (range finding study)

TEST MATERIAL: Technical piperonyl butoxide, FEP 100, stated
purity: 90.78%.

STUDY NUMBER(S): 542-005

SPONSOR: Piperonyl Butoxide Task Force

TESTING FACILITY: International Research and Development
Corporation, Mattawan, Michigan

TITLE OF REPORT: "Evaluation of Piperonyl Butoxide in a One Year
Chronic Dietary Toxicity Study in Dogs"

AUTHOR: Edwin I. Goldenthal

REPORT ISSUED: September 9, 1993 (Study dates: May 15, 1991 to May
15, 1993 (necropsy date).

EXECUTIVE SUMMARY:

Four groups of 4/sex beagle dogs were dosed with 0 (controls), 100, 600 or 2000 ppm diets containing piperonyl butoxide (PBO, 90.78% purity but as 100% a.i.) for one year. These doses correspond to 2.9, 15.5 or 52.8 mg/kg/day PBO in males and 2.7, 16.3 or 71.0 mg/kg/day PBO in females. The dogs were assessed daily for reactions and weekly and later biweekly for body weight and food consumption. Clinical hematology, chemistry and urinalysis were assessed at 6 months and termination and organ weights and pathology were assessed at termination.

Reactions to treatment were noted at 600 ppm and above. At 600 ppm there was decreased body weight gain with males gaining only 16% in the mid and 3% in the high dose groups while controls gained 24.8% and females in the mid dose gaining only 19.8% and high dose showing a decrease in weight gain of 2% whereas the controls gained 21.8%. Decreases in food consumption paralleled

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(83-1 (dog). Piperonyl butoxide/1993)

the body weight changes in males but not females. At 2000 ppm, serum alkaline phosphatase was elevated in males (340% at 6 months and >500% at 1 year) and females (368% at 6 months and >600% at 1 year). Mid dose group males were elevated about 60% at each interval but not significantly. Terminal high dose group liver weight was also increased in males (22% absolute and 52% relative) and females (36% absolute and 86% relative). Elevations in female liver weight (12% absolute and 13% relative) were also apparent. The high dose males (3/4) and females (all 4) had hepatocellular hypertrophy, a condition not reported in any other test groups. The LEL is 600 ppm based on decreases in body weight gain in both sexes with trends for increased alkaline phosphatase and liver weight noted. The NOEL is at 100 ppm.

Classification: CORE-GUIDELINE. The study satisfies the requirement for a series 83-1(b) chronic feeding study in non-rodents. No additional series 83-1(b) study data are required at this time.

Quality Assurance Statement: Provided

Good Laboratory Practice Statement: Provided.

[Note. The GLP statement refers to comments on the conduct in the study as being in Appendix B. These were actually found in appendix M. TB-I concurs that the deviations from the protocol do not affect the integrity of the study.

Statement of No Data Confidentiality Claim: Provided.

Review

Experimental Constants:

Test Chemical:

Chemical:	Technical grade piperonyl butoxide (FEP 100)
Lot:	None provided (see below under Test Chemical Analysis A.
Purity:	90.78% purity (as per sponsor's certificate)
Source:	Fairfield American Corporation, Middleport, New Jersey.
Description:	Yellow liquid
Storage:	Ambient temperature in an environmentally controlled area.

Test Chemical Analysis:

A. Analysis of the test material. A certificate of analysis provided by the sponsor indicated the test material to be 90.6% piperonyl butoxide. Although no lot number is provided, the certificate of analysis assures the identity of the product.

B. Homogeneity in the diet. Samples of the top, middle and bottom were assessed for the 100 and 2000 ppm test diets. These yielded sample means of 96.6 ppm with a coefficient of variation of 1.1% and 1980 ppm with a c.v of 1.8%. Thus indicating satisfactory homogeneity.

[83-1 (dog). Piperonyl butoxide/1993]

C. Stability in the diet. Samples of test diets prepared at 100, 600 and 2000 ppm dose levels were assessed to have 100%, 101% and 97% of PBO after 30 days of storage.

D. Concentration in the diet. Mean values for 16 diet preparations indicated 94.9 ± 4.9 , 590 ± 20 and 1960 ± 48 ppm for the 100, 600 and 2000 ppm test diets respectively.

Test System:

Species:	Pure bred beagle dogs
Source:	Ridglen Farms, Mt. Horeb, Wisconsin
Age:	5 to 6 months of age at time of receipt.
Weight:	Males 10.6 to 14.3 kg, females 7.2 to 12.3 kg.
Housed:	Individually
Diet:	Certified Canine Chow, Ralston Purina Co., Fresh diets containing the test material were prepared weekly.

The dogs were immunized for several diseases at the breeders facilities.

Basic Study Design:

Four groups of 4 dogs/sex were dosed with 0 (control), 100, 600 or 2000 ppm of piperonyl butoxide (adjusted to 100% from 90.78% purity) in their diets for one year.

The dose levels were selected based on the results of a preliminary range finding study (MRID No.: 429260-01, IRDC #542-004, Sept. 9, 1993, no DER has been prepared for this study). In this study, 2 beagle dogs/sex were dosed with 0, 500, 1000, 2000 and 3000 ppm piperonyl butoxide for 8 weeks. The dogs dosed with 3000 ppm were noted to eat less and lose weight and have increased liver and gall-bladder weight and have hypertrophy of the hepatocytes. Other possible compound related changes noted at 2000 ppm and above included increases in alkaline phosphatase, decrease in cholesterol and decreased testicular/epididymal weight.

4. Statistics - The following procedures were utilized in analyzing the numerical data:

Statistical Test	Parameters
<p>Bartlett's test for homogeneity of variance. ANOVAR (one-way classification).</p> <p>Significance of differences were also assessed by comparing treatment groups to the control by sex using the "appropriate" t-statistic (for equal or unequal variance). Dunnett's multiple comparison tables or pairwise comparisons with a Bonferroni correction were also used to determine the significance of differences.</p>	<p>Body weights, food consumption, hematological, biochemical and urological parameters, and absolute and relative organ weights.</p>
<p>Conover and Iman method of transforming the data into ranks prior to analysis.</p>	<p>Non-parametric data</p>

SPECIFIC METHODS AND RESULTS

1. Survival and clinical signs. The dogs were reported to be inspected twice daily for signs of moribundity and overt toxicity and detailed clinical observations were stated to be conducted at least twice weekly.

No dogs died. There were no clinical signs attributed to the test material reported.

2. Body weight, feed consumption and compound intake. Body weight and feed consumption were determined weekly during the first 14 weeks and biweekly thereafter. Individual test article consumption was determined weekly based on body weight and feed consumption. The study report asserts that both males and females had reduced bodyweight in the 600 and 2000 ppm dose groups. Table 1 illustrates the effects on body weight.

Table 1. Body weight and compound (PBO) consumption.

Group	Males			Females		
	Initial/Final (kgms) (mg/kg/day)	Gain ² (%)	PBO ³	Initial/Final (kgms)	Gain (%)	PBO mg/kg/day
Control	13.3/16.6	+24.8	--	11.0/13.4	+21.8	--
100 ppm	13.2/16.0	+21.2	2.9	10.9/13.6	+24.8	2.7
600 ppm	13.1/15.2	+16.0	15.5	10.6/12.7	+19.8	16.3
2000 ppm	13.1/13.5	+3.1	52.8	10.2/10.0	-2.0	71.0

Body weight data from page 26 and Table 2 pages 45 to 48 of the study report.
PBO consumption data from page 27 and Table 4 pages 55 to 58 of the study report.

1. Initial and final body weight in kgs.
2. Percent difference in weight from initial weight, an index of weight gain.
3. Mean PBO consumed in mg/kg/day based on feed consumption and body weight.

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In addition to the obvious effects noted for decreases in body weight in the 600 and 2000 ppm dose groups, inspection of Figure 1 of the study report indicates that the 100 ppm male dose group consistently had decreased body weight from about week 7 to study termination. This weight difference was less than 5% and did not reach statistical significance.

Paralleling the decreased weight gain in males, there were decreases (not statistically significant) in mean feed consumption of 1.4, 15.4 and 19.5% for the low, mid and high dose groups when compared to the controls. Female mean feed consumption data did not parallel the body weight of the dogs with there being decreases of 9, 13.2 and 6.9% for the low, mid and high dose groups respectively. The study report does not consider the differences in feed consumption in females to be related to the test material. TB-1 would expect the feed consumption to parallel the body weight gain decrease. The limited number of dogs/group is probably confounding the pattern of food consumption.

Mean daily compound consumption was determined and the results are tabulated in Table 1 above.

Note: There is an ambiguity in the study report which indicated that compound consumption was determined weekly. If body weight and food consumption data were determined every two weeks, then the food consumption could not have been determined weekly but only at biweekly intervals. Table 4 of the study report which lists the test consumption data is more consistent with the biweekly determination of body weight and feed consumption since after week 14, biweekly values are presented.

CONCLUSION (body Weight): NOEL and LEL = 100 and 600 ppm. At 600 ppm, male and female body weight gain is decreased.

Note: TB-I recognizes that the 100 ppm dose group in males may be a threshold effect level but there is insufficient data to conclude that this level is definitely affected. There are too few dogs per dose group to be more conclusive.

3. Ophthalmological examinations. The dogs were assessed for ocular effects at pretest and at week 52. The study report asserts that there were no compound related effects. The study report did not include the individual animal data and TB-I does not consider it necessary in the absence of suspected effects.

4. Hematology and Clinical Chemistry. Blood was collected from the jugular vein after overnight fasting before treatment, at 6 months and at study termination for hematology and clinical analysis.

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[83-1 (dog). Piperonyl butoxide/1993]

a. Hematology

- | | |
|--|--|
| <p>X
 <input checked="" type="checkbox"/> Hematocrit (HCT)
 <input checked="" type="checkbox"/> Hemoglobin (HGB)
 <input checked="" type="checkbox"/> Leukocyte count (WBC)
 <input checked="" type="checkbox"/> Erythrocyte count (RBC)
 <input checked="" type="checkbox"/> Platelet count</p> | <p>X
 <input checked="" type="checkbox"/> Leukocyte differential count
 <input checked="" type="checkbox"/> Mean corpuscular HGB (MCH)
 <input checked="" type="checkbox"/> Mean corpuscular HGB conc. (MCHC)
 <input checked="" type="checkbox"/> Mean corpuscular volume (MCV)
 <input checked="" type="checkbox"/> Reticulocyte count</p> |
|--|--|

The study report asserts that there were no effects on the hematological parameters investigated. Inspection of Table 5 of the study report indicates that at the 6 month interval erythrocytes (13% (p < 0.05) were less in the male high dose group than in the controls. At 1 year this group was also 13% lower but not statistically significant. TB-I does not consider this a definite effect of the test material since blood cell count can vary and only 4 dogs were used for each dose group.

b. Clinical Chemistry

- | | |
|--|--|
| <p>X
 Electrolytes:
 <input checked="" type="checkbox"/> Calcium
 <input checked="" type="checkbox"/> Chloride
 <input checked="" type="checkbox"/> Magnesium
 <input checked="" type="checkbox"/> Phosphorous
 <input checked="" type="checkbox"/> Potassium
 <input checked="" type="checkbox"/> Sodium
 Enzymes
 <input checked="" type="checkbox"/> Alkaline phosphatase
 <input checked="" type="checkbox"/> Cholinesterase
 <input checked="" type="checkbox"/> Creatinine phosphokinase
 <input checked="" type="checkbox"/> Lactic acid dehydrogenase
 <input checked="" type="checkbox"/> Serum alanine aminotransferase (also SGPT)
 <input checked="" type="checkbox"/> Serum aspartate aminotransferase (also SGOT)
 <input checked="" type="checkbox"/> gamma glutamyl transferase
 <input checked="" type="checkbox"/> glutamate dehydrogenase</p> | <p>X
 Other:
 <input checked="" type="checkbox"/> Albumin
 <input checked="" type="checkbox"/> Blood creatinine
 <input checked="" type="checkbox"/> Blood urea nitrogen
 <input checked="" type="checkbox"/> Cholesterol*
 <input checked="" type="checkbox"/> Globulins
 <input checked="" type="checkbox"/> Glucose*
 <input checked="" type="checkbox"/> Total Bilirubin*
 <input checked="" type="checkbox"/> Total Serum Protein*
 <input checked="" type="checkbox"/> Triglycerides
 <input checked="" type="checkbox"/> Serum protein electrophoresis</p> |
|--|--|

The study report asserts that there were increases in alkaline phosphatase in the high dose group males and females at both time intervals. Table 2 below indicates the increases in this enzyme noted.

Table 2. Alkaline phosphatase activity in dogs dosed with piperonyl butoxide for one year.

Group	Males ¹		Females	
	6 months	12 months	6 months	12 months
Control	45 ± 6.4	36 ± 6.2	60 ± 10.5	49 ± 14.9
100 ppm	55 ± 10.2 (22%)	47 ± 20.1 (31%)	90 ± 52.5 (33%)	71 ± 38.9 (45%)
600 ppm	72 ± 19.3 (60%)	59 ± 19.0 (64%)	46 ± 10.7 (-23%)	44 ± 9.2 (-10%)
2000 ppm	153 ± 41.9 (340%)*	194 ± 61.2 (539%)*	221 ± 53.7 (368%)	300 ± 97.4 (612%)*

Data are from Table 6 of the study report.

1. Units are International Units/liter.

* statistically difference from control p < 0.05

The above data indicate that at the high dose, large increases (>500%) in alkaline phosphatase are noted. In males, although the differences are not statistically significant, there is a trend for increased enzyme activity in the mid dose group (about 60% increased at both assessment times). It is possible that liver damage (the probable source of the increased enzyme level in the blood) is starting to occur at the lower dose levels. There is, however, no support for this in the females since the mid dose level is decreased relative to the control.

Serum cholesterol was noted to be decreased in some assessments (i.e. maximum in males -20% at termination, and maximum in females about 50% at termination) for all dose groups but not statistically significantly. Large standard deviations (about 50% of the mean) in the control group confounded the interpretation of the data. It is, however, possible that the decreased cholesterol values were tied in with the liver changes noted.

c. Urinalysis. Urine was collected from fasted animals at pretest, 6 months and at study termination. The CHECKED (X) parameters were examined.

X		X	
x	Appearance	x	Glucose
	Volume	x	Ketones
	Specific gravity	x	Bilirubin
	pH	x	Blood
x	Sediment (microscopic)	x	Nitrites
x	Protein	x	Urobilinogen

The study report asserts that there were no effects on these parameters at either time of assessment.

CONCLUSION (hematology, clinical chemistry and urinalysis): NOEL and LEL = 600 and 2000 ppm. At 2000 ppm definite increases in alkaline phosphatase. Trends for increased activity may be evident in the mid dose male groups.

Terminal Studies Pathology

After one year of dosing, the dogs were euthanized with sodium pentobarbital followed by exsanguination, necropsied, and organs weighed and prepared for histopathology.

No treatment related lesions were indicated at necropsy.

a. Organ weights.

The following organs were weighted:

- | | |
|-----------------------------------|-------------------------------|
| x adrenals (2) | x brain (with stem) |
| x heart | x kidney (2) |
| x liver with drained gallbladder | x ovary |
| x pituitary | x testis with epididymis (2) |
| x thyroid/parathyroid (2) | |

The liver and thyroid/parathyroid were noted to have weight deviations and these are discussed in the individual organ discussions below.

b. Histopathology The following organs/tissues were prepared for histological assessment.

- | | | | |
|--------------------|----------------------|---------------------------|---|
| | X | | X |
| Digestive system | Cardiovasc./Hemat. | Neurologic | |
| x Tongue | x Aorta | x Brain | |
| x Salivary glands | x Heart | x Periph. nerve | |
| x Esophagus | x Bone marrow*(rib) | x Spinal cord (3 levels) | |
| x Stomach | x Lymph nodes | x Pituitary | |
| x Duodenum | x Spleen | x Eyes (optic n.) | |
| x Jejunum | x Thymus | Glandular | |
| x Ileum | Urogenital | x Adrenals | |
| x Cecum | x Kidneys | x Lacrimal gland | |
| x Colon | x Urinary bladder | x Mammary gland | |
| x Rectum | x Testes | x Parathyroids | |
| x Liver | x Epididymides | x Thyroids | |
| x Gall bladder | x Prostate | Other | |
| x Pancreas | Seminal vesicle | x Bone | |
| Respiratory | x Ovaries | x Skeletal muscle | |
| x Trachea | x Uterus | x Skin | |
| x Lung | | x sternum | |

and gross lesions.

The tissues were fixed in buffered formalin and although the stain used was not mentioned it is assumed to be hematoxylin and eosin.

The following organs/tissues are discussed individually.

A. Liver. Liver weight was increased (both absolute and relative) in the high dose group as indicated in the Table 3.

Table 3. Liver weight in dogs dosed with piperonyl butoxide for one year.

Group	Males		Females	
	Absolute ¹	Relative ²	Absolute	Relative
Control	362.5±73.2	2.29±0.28	292.9±68.4	2.26±0.22
100 ppm	362.9±21.0	2.34±0.44 (2%)	285.7±54.6	2.22±0.33
600 ppm	374.6±19.2 (3%)	2.58±0.06 (13%)	328.6±57.0 (12%)	2.69±0.31 (19%)
2000 ppm	442.0±39.0 (22%)	3.49±0.55 (52%)*	397.5±58.3 (36%)	4.21±0.39 (86%)

Data are from Table 9 of the study report pages 76 to 87.

1. Liver weight in grams.

2. Liver weight relative to body weight.

* Statistically significant $p < 0.05$.

Liver weight was also expressed as relative to brain weight and similar increases were noted but there was still no statistical significance in the mid dose group.

Hepatocyte hypertrophy (described as mild) was found only in the high dose group animals. Three of the four males and all four females had this condition. This condition was further described as the cytoplasm of the hepatocytes having a ground glass appearance and stained slightly paler than normal in hematoxylin and eosin sections. In addition to the liver weight and hypertrophy, serum alkaline phosphatase (an indicator of liver damage) was also increased see above Table 2. These data establish the liver as a target organ of PBO in the dog.

B. Thyroid/parathyroid.

Females in the 2000 ppm dose group had apparent increases in the left (34%) and right (35%) thyroid/parathyroid weights. A part of Table 9 from the study report is appended to illustrate the thyroid/parathyroid weight data. Increases in thyroid/parathyroid body weight ratios (83%) were also evident. Inspection of the data indicate that the low and mid dose groups were also higher than the controls but not in a dose related manner. There were no histopathological findings in the thyroid/parathyroids of either sex. TB-I does not consider the weight changes in the thyroid/parathyroid to be definitely compound related. The standard deviations were high and there are too few dogs/dose level to make a more definite assessment and they were not accompanied by pathological changes.

C. Gall-bladder weight was decreased in the range finding study. Gall-bladder weight was included with liver weight above. It was not determined if the gall bladder itself was affected. The only pathological finding in the gall bladders was a cyst (mild) in the high dose male group.

D. Testis. Testicular weights were reduced in the range finding study but there were no effects on the weight in the main study.

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[83-1 (dog). Piperonyl butoxide/1993]

The mid and high dose groups each had one animal with mild atrophy of the testis and this condition was not found in the controls. TB-I notes the presence of the atrophy but declines from concluding it is definitely compound related.

CONCLUSION/DISCUSSION: This study is classified as CORE GUIDELINE. The study established the liver as the primary target organ in dogs based on liver weight decreases and increases in serum alkaline phosphatase and the presence of hypertrophy all at the high dose level. Trends (non-statistically significant increases) for increased alkaline phosphatase and increased liver weight were evident in the mid dose group but the few number (4/sex/dose group) of dogs on the study precluded more definite conclusions that these trends were actually effects of the test material. The study supports a NOEL and LEL of 100 and 600 ppm based on decreased body weight gain and the presence of trends for increased alkaline phosphatase and liver weight.

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TABLE 9 Cont. Females: Summary of Organ Weight Values - Terminal Sacrifice

Parameters Measured	0 ppm (Control)		100 ppm		600 ppm		2,000 ppm	
	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.
Thyroid/Parathyroid, Left 9	0.59	0.070	0.72	0.298	0.75	0.195	0.79	0.209
Thyroid/Parathyroid, Left/Body Weight $\times 10^3$	4.63	0.787	5.35	1.692	6.08	1.241	8.22 ²	1.274
Thyroid/Parathyroid, Left/Brain Weight $\times 10^2$	74.13	9.586	92.98	43.301	92.80	24.049	100.78	21.119
Thyroid/Parathyroid, Right 9	0.63	0.091	0.67	0.202	0.68	0.113	0.85	0.180
Thyroid/Parathyroid, Right/Body Weight $\times 10^3$	4.90	0.780	5.06	0.573	5.56	0.829	8.99 ²	1.744
Thyroid/Parathyroid, Right/Brain Weight $\times 10^2$	78.63	9.758	86.17	27.108	83.89	12.488	108.89	16.332

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²Significantly different from the Control group: $\mu \leq 0.01$

S.D. - Standard Deviation
N - Number of Animals

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