Translation from Japanese Original Report (Text and tables only)

13-week subacute toxicity study of CGA-48988 in rats

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Translation: January 2005

Original Japanese Report Issue Date: March 2, 1982

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I Summary

A 13-week subacute toxicity study of CGA-48988 [DL-N-(2,6-dimethylphenyl)-N-(2'-methoxyacetyl)alaninemethylester] was conducted with male and female JCL:SD rats to which the test substance was administered with food at a concentration of 0, 50, 250, 1250 and 9375 ppm. 20 male and 20 female rats per treatment group were used.

1. No poisoning symptom related to treatment with CGA-48988 was observed and no animal died.
2. Decreased weight gain was observed in female animals of the 1250 and 9375-ppm treatment groups and in male animals of the 9375-ppm treatment group. No remarkable change was observed in the 50 or 250-ppm treatment groups.
3. Avoidance of eating was observed in male and female animals of the 9375-ppm treatment group immediately after the initiation of treatment, however, food consumption increased to almost the same level as that of the control group at 7 days after initiation of treatment. Subsequently, in female animals of that group, decreases in food consumption were continuously observed, and slightly decreased food consumption was also observed in female rats of the 1250-ppm group.

   Food efficiency was calculated at 5 and 13 weeks after the initiation of treatment. It was low in female animals of the 9375-ppm treatment group at both time points. It was slightly lower in male animals of the 9375-ppm treatment group and in female animals of the 1250-ppm treatment group. The decreased weight gain described above was considered to be mainly due to decreased food efficiency as well as decreased food consumption.
4. Water consumption was low in female animals of the 9375-ppm treatment group, and was particularly remarkable at the time when food consumption was low.
5. Hematology revealed decreased red blood cell counts (females), low hematocrit values (males and females) and low hemoglobin contents (males) in the 9375-ppm treatment group, indicating anemia. However, no evident effect of CGA-48988 treatment was confirmed since no change in reticulocyte counts was observed.
6. Biochemistry revealed increased cholesterol levels and decreased A/G ratios in male animals of the 9375-ppm treatment group, suggesting an effect of CGA-48988 on the liver.

   In female animals of the 9375-ppm treatment group, increased values of cholesterol and blood glucose and decreased values of A/G ratios and total protein due to decreased albumin levels were observed, indicating an effect of CGA-48988 on the liver as well as the effect of malnutrition.
7. Urinalysis revealed no change attributable to CGA-48988 treatment.

8. Liver weight and its ratio to body weight increased in male and female animals of the 9375-ppm treatment group. The increase in the ratio of liver weight to body weight observed in male and female animals of the 1250-ppm treatment group might also be attributable to the treatment with CGA-48988.

9. Necropsy and histopathological examination revealed no change attributable to CGA-48988 treatment.

10. The maximum no-observed-effect level and the lowest-observed-adverse-effect level of CGA-48988 in JCL: SD rats were considered as follows, based on the above results.

	Male	Female
Maximum no-observed-effect level	250 ppm (15.61 mg/kg/day)	250 ppm (17.48 mg/kg/day)
Lowest-observed-adverse-effect level	1250 ppm (79.81 mg/kg/day)	1250 ppm (86.96 mg/kg/day)

II Test substance

The test substance used in this study was identified as follows.

1. Name of Test substance

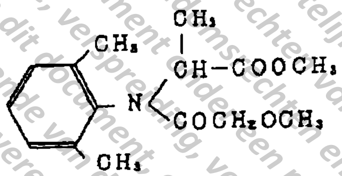
   CGA-48988

2. Chemical name and structural formula

   Chemical name:

   DL-N-(2, -dimethylphenyl)-N-(2’-2’-methoxyacetyl)alaninemethylester

   Structural formula:



3. Description

   1) Color and Appearance : Light brown powder
   2) Odor : Aromatic odor
   3) Melting point : 71.8-72.3°C
   4) Relative density : 1.21 (20°C)
   5) Solubility : 0.71% in water (20°C)

      Soluble in organic solvent such as methanol, methylenechloride and benzene

4. Stability

   Half life: 200 days or longer at 50°C at pH 5 and 7

5. Lot number and purity

   Lot. No.: EN32212

   Purity: 94.1%

6. Supplier

   Ciba-Geigy Japan Co., Ltd.

   2-4-1 Hamamatsu-cho, Minato-Ku, Tokyo (in the World Trade Center Building)

III Study methods

1. Study period

For 13 weeks from July 13, 1981 to October 13, 1981

2. Test animals

Male and female JCL: SD rats aged 4 weeks were purchased from Clea Japan, Inc. and acclimatized for one week at our laboratories. Only healthy animals showing satisfactory growth during the acclimation period were selected and used for the study.

The body weights of male and female rats at initiation of the study were within a range of 150-180 g and a range of 130-160 g, respectively.

The acclimation and the study were conducted in a BS (Barrier System) animal room with the conditions controlled at a room temperature of 22 ± 2°C, humidity of 55 ± 5% and a light/dark cycle of 12 hours (lighting from 7:00 to 19:00).

Animals were housed in groups of two in a stainless-steel mesh cages (260 W × 205 D × 180 H mm). The cages were replaced once with clean cages once a week.

The animals were fed a powder diet CE-2 (Clea Japan, Inc.) with the test substance CGA-48988 and given free access to water by using a polycarbonate water bottle. The feeder and water bottle were replaced once a week.

3. Doses and Group composition

Doses of CGA-48988 and the number of animals are shown in Table 1.

The doses of CGA-48988 were established based on the results of a preceding subacute toxicity study (Geigy-Pharmaceuticals: Unpublished).

The highest dose was established at a concentration of 9375 ppm in food so that the subacute toxicity of CGA-48988 could be fully assessed, followed by 1250, 250 and 50 ppm. There were 4 dose levels in total.

The animals in the control group were given free access to the powder diet CE-2 without CGA-48988. The study was initiated with 20 males and 20 females per group, and the tests were conducted for all of the live animals at 13 weeks after initiation of treatment.

4. Administration method

CGA-48988 was administered with food for 13 weeks.

The test substance and a small amount of the powder diet were mixed in a mortar with acetone as a solvent. Then, the powder diet was added so that the concentrations designated for this study could be prepared and blended using a ball mill. The diet used for the control group had only acetone added. The diet preparation was conducted on the weekly basis, and the prepared diet

was stored in a refrigerator (2-6°C) until the use. The diet food remaining after one week following preparation was discarded.

A 200 g of the diet prepared at each concentration was sampled at four week interval, and was sent to the sponsor and the concentrations were analyzed at the Japan Food Research Laboratory (52-1 Motoyoyogi-machi, Shibuya-Ku, Tokyo). Of the sample for the second analysis, 50-ppm and 9375-ppm diets were used for the determination of stability at room temperature. The analytical results are summarized as follows. The complete results are attached at the end of this report (Appendix J).

Determination of Concentrations

Day of preparation / Concentrations prepared	July 21	August 18	September 16
0 ppm	< 10.0	< 10.0	< 10.0
50	50.2	44.8	49.7
250	258	234	235
1250	1050	1020	1100
9375	8920	7800	8060

Stability of the diet for one week at room temperature

Concentrations prepared	Immediately after preparation	One week after preparation
50 ppm	44.8 ppm	37.8 ppm
9375	7800	7580

5. Observation items

1) General signs and mortality

The animals were observed for any unusual signs, and the presence or absence of dead animals was confirmed every day.

2) Determination of body weight

Male and female animals were weighed twice a week from the day of initiation of treatment to 13 weeks of treatment.

3) Food consumption and test substance intake

Food consumption was determined twice a week from the day of initiation of treatment by weighing the cage (total weight of two animals) and converted into the weight per animal per day. Test substance intake was also calculated in the usual manner.

4) Food efficiency

Food efficiency was obtained at 5 and 13 weeks after initiation of treatment by dividing weight gain of each animal by the food

consumption during the time period.

5) Water consumption

Water consumption per cage (total amount for two animals) was determined every week from the day of initiation to the completion of treatment and converted into the amount per animal per day.

6) Hematology

Blood was collected (anticoagulant: EDTA-2K) from the caudal vein of each animal at the completion of the 13-week treatment and subjected to the following tests.

Red blood cell counts and white blood cell counts (Neubauer hemocytometer method), hematocrit values (capillary centrifugal method), hemoglobin contents (cyanmethemoglobin method), platelet counts (Fonio method), differential counts of leukocytes (Pappenheim's staining) and reticulocyte counts (Brecher method) were determined.

Mean corpuscular hemoglobin (MCH), mean cell volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) were also calculated.

7) Biochemistry

The chest of the animals was opened under ether anesthesia after fasting for 24 hours following the completion of the 13-week treatment. Serum was obtained by cardiocentesis and used for the following tests.

GOT and GPT (Reitman-Frankel method), alkaline phosphatase (Kind-King method), blood glucose (O-aminobiphenyl method), total protein (refractometry), urea nitrogen (direct colorimetry of diacetyl monooxime), cholesterol (Zurkowski method), Na and K (flame photometry), chloride (mercury nitrate titration), creatinine (Folin-Wu method) and albumin (HABCA method) were determined. A/G ratios were also calculated.

8) Urinalysis

12-hour urine was collected using a cage for urine sampling at the completion of the 13-week treatment, and urine volume was determined. Half of the urine was centrifuged, and the supernatant was used for the following tests.

Tests for occult blood, ketone bodies, urinary sugar, protein, pH and urobilinogen were conducted using Urolabsticks (Miles-Sankyo), and qualitative reaction of bilirubin was done by using Ictsticks (Miles-Sankyo).

The remaining urine was used for determining specific gravity (refractometry), Na and K (flame photometry), and sediment (light microscopy).

9) Organ weights and Histopathology

Animals used in this study were exsanguinated at the completion of the 13-week treatment, and macroscopic examination of organs and tissues was conducted.

The following organs were isolated and weighed. Then, the ratio of the organ weight to the body weight was calculated from the body weight of each animal determined at the completion of the treatment.

Brain, heart, lung, liver, spleen, kidney, adrenal gland, thymus gland, thyroid gland, pituitary gland, pancreas, testicle, seminal vesicle, prostate gland, uterus and ovary.

Paraffin sections of stomach, small intestine, large intestine, mesenteric lymph node, esophagus, trachea, skeletal muscle (thigh muscle), bone marrow (Os femoris), sciatic nerve, spinal cord, skin, salivary gland, mammary gland (only females), epididymis and gross lesions, as well as the above organs, were prepared in the usual manner, stained with hematoxylin-eosin and subjected to light microscopy.

10) Statistical tests

Differences in mean values between the control group and each treatment group were statistically examined. Actual measurement values of body weights, hematological parameters, biochemical parameters, some urine parameters and organ weights were tested with Student t-test, and the frequency of pathological findings was tested with χ^2 test.

When a significant difference was observed, a mark of * ($p < 0.05$), ** ($p < 0.01$) or ***($p < 0.001$) was attached to the corresponding value in each table.

IV Results

1. General signs and mortality

(Fig. 1 and Table 2)

There were no unusual general signs related to treatment with the test substance during the study period. No animals died in any treatment group.

2. Changes in body weight

(Figs. 2 and 3, and Tables 3 and 4)

Changes in mean body weight during the study period are shown in Figs. 2 and 3, and Tables 3 and 4.

In male animals, decreased weight gain was observed in the 9375-ppm treatment group from 3 days after initiation of treatment to the completion of treatment.

In female animals, decreased weigh gain was observed in the 9375-ppm treatment group from 3 days after initiation of treatment and in the 1250-ppm treatment groups from 66 days after initiation of treatment to the completion of treatment.

No change in body weight was observed in male or female animals of the 50 and 250-ppm treatment groups, nor in male animals of the 1250-ppm treatment group.

3. Food consumption and test substance intake

(Figs. 4 and 5, and Tables 5, 6, 7, 8 and 9)

Food consumption during the study period is shown in Figs. 4 and 5, and Tables 5 and 6.

In male animals, markedly decreased food consumption was observed in the 9375-ppm treatment group from the day of initiation of treatment, however, it had considerably recovered at 7 days after initiation of treatment. There was no remarkable difference in food consumption between the control group and this treatment group after that time.

In female animals, markedly decreased food consumption was also observed in the 9375-ppm treatment group from the day of initiation of treatment, however, it had considerably recovered at 7 days of treatment, as with the male animals. But the decreased food consumption was then continuously observed until the completion of treatment. Slightly decreased food consumption was also observed in female animals of the 1250-ppm treatment group.

No abnormal finding was observed in the male and female animals of the 50 and 250-ppm treatment groups nor in male animals of the 1250-ppm treatment group. Test substance intake calculated from food consumption is shown in Table 7, 8 and 9.

4. Food efficiency

(Table 10)

Food efficiency for 5 weeks and 13 weeks after the initiation of treatment is shown in Table 10.

Food efficiency for 5 weeks was markedly low in female animals of the 9375-ppm treatment group. Food efficiency for 13 weeks was also markedly low in female animals of the 9375-ppm treatment group and slightly low in male animals of the 9375-ppm treatment group and female animals of the 1250-ppm treatment group. The efficiency observed in male and female animals of the other treatment groups was comparable to that of the control group.

5. Water consumption

(Figs. 6 and 7, and Tables 11 and 12)

Water consumption during the study period is shown in Figs. 6 and 7 and Tables 11 and 12.

An increase in water consumption was observed until one week after initiation of treatment in male and female animals of the 9375-ppm treatment group. No remarkable change was observed in male animals after that, however, water consumption was low in female animals of the 9375-ppm treatment group from 4 weeks after initiation of treatment.

6. Hematology

(Table 13)

The results of the hematological examination conducted at the completion of treatment are shown in Table 13.

Male animals of the 9375-ppm treatment group showed lower hematocrit values and hemoglobin contents compared with those of the control group. Leukocyte classification showed an increase in the percentage of lymphocytes.

Female animals of the 9375-ppm treatment group showed lower red blood cell counts and hematocrit values compared with those of the control group. Leukocyte classification showed an increase in the percentage of lymphocytes.

There was no difference in the values of the other parameters between any treatment group and the control group.

7. Biochemistry

(Table 14)

The results of the biochemical examination conducted at the completion of treatment are shown in Table 14.

Male animals of the 9375-ppm treatment group showed higher values of cholesterol and potassium and lower A/G ratios compared with those of the control group.

Female animals of the 9375-ppm treatment group showed higher values of blood glucose and cholesterol and lower values of total protein, A/G ratios and albumin compared with those of the control group.

There was no remarkable change in the other parameters for male and female animals of any treatment group.

8. Urinalysis

(Table 15)

The results of urinalysis conducted at the completion of treatment are shown in Table 15.

Male animals of the 9375-ppm treatment group showed a greater volume of urine and lower values of sodium and relative density compared with those of the control group.

Female animals of the 9375-ppm treatment group showed a high value of potassium.

No remarkable change in the other parameters was observed in any treatment group.

9. Organ weight

(Tables 16 and 17)

Organ weight and the ratio of organ weight to body weight at the completion of the treatment are shown in Tables 16 and 17.

In male animals, decreased lung weight was observed in the 1250 and 9375-ppm treatment groups, however, ratios to body weight in both groups were comparable to that of the control group. Increased liver weight was observed in the 9375-ppm treatment group and an increased ratio to body weight was observed in the 1250 and 9375-ppm treatment groups. An increased ratio in the weight of the kidney (both sides), testicle (one side) and adrenal gland (one side) to body weight was observed in the 9375-ppm treatment group.

In female animals, increased liver weight was observed in the 9375-ppm treatment group, and an increased ratio to body weight was observed in the 1250 and 9375-ppm treatment groups. Decreased weights for the heart, lung and kidney (both sides) were observed in the 1250 and 9375-ppm treatment groups. The ratio of the weight of these organs, as well as that of the brain, uterus, adrenal gland (one side), pituitary gland and pancreas, to body weight was high in the 9375-ppm treatment group. An increase in the ratio of the brain weight to body weight was also observed in the 1250-ppm treatment group.

10. Necropsy and Histopathology

1) Macroscopic finding

(Table 18)

Macroscopic findings obtained at the completion of treatment are summarized in Table 18.

In male animals, congestion and petechial bleeding in the lungs, nodules in the liver, and cyst formation in the kidney were observed in all of the

treatment groups. In addition, localized fatty-like changes and hemorrhage in the pancreas, hematoma-like changes in the pituitary gland, hemorrhage in the thymus gland and swelling of the mesenteric lymph nodes were observed. All of these findings were isolated cases.

In female animals, congestion of the lungs and cyst-like changes or hematoma in the ovary were observed in the control group and all of the treatment groups, and hemorrhage in the thymus gland was observed in the 50-ppm treatment group. Retention of clear fluid in the uterus was observed in all of the treatment groups except the 1250-ppm treatment group. Its frequency was high in the 9375-ppm treatment group, showing a statistically significant difference from that of the other group.

2) Histopathological findings

(Table 19)

The results of histopathological examination of organs and tissues removed from the test animals at the completion of treatment are summarized in Table 19. A summary of the results follows.

Lung : Hyperplasia of the alveolar wall was observed in male and female animals of the control group and each treatment group at a relatively high frequency. Hemorrhage was observed in one male animal of the 250-ppm treatment group.

Liver : Localized necrosis was observed in one male each of the 250 and 9375-ppm treatment groups.

Kidney : Cyst formation in one male of the 50-ppm treatment group; calcareous deposit in one female each of the control, 50 and 9375-ppm treatment groups; and pyelonephritis in one male of the 50-ppm treatment group and in one female of the 9375-ppm treatment group were observed.

Pituitary gland : Mild congestion was observed in one male animal of the 9375-ppm treatment group.

Thymus gland : Hemorrhage was observed in one female animal of the 50-ppm treatment group.

Mammary gland : Cyst formation was observed in one female animal of the 9375-ppm treatment group.

Ovary : Congestion in one female each of the control and the 1250-ppm treatment groups; follicular cysts in one female of the 1250-ppm treatment group; and luteal hypoplasia in one female each of all the treatment groups were observed.

Uterus : Dilation of uterine lumen was observed in one to 6 animals of the control group and each treatment group.

V Discussion

A 13-week subacute toxicity study of CGA-48988 [DL-N-(2,6-dimethylphenyl)-N-(2'-methoxyacetyl) alaninemethylester] was conducted with male and female JCL:SD rats to which the test substance was administered with food at a concentration of 0, 50, 250, 1250 and 9375 ppm.

No remarkable or unusual symptom was observed in the male and female animals of any treatment group during the 13-week treatment period, and no animal died throughout the study period.

Decreased weight gain was observed in female animals of the 1250-ppm treatment group and in male and female animals of the 9375-ppm treatment group.

In male and female animals of the 9375-ppm treatment group, markedly decreased weight gain was observed immediately after initiation of treatment and persisted throughout the study period.

A tendency to avoid eating was observed immediately after initiation of treatment in male and female animals of the 9375-ppm treatment group. However, the tendency soon disappeared. In female animals of the 9375 and 1250-ppm treatment groups, decreased food consumption was continuously observed.

Food efficiency was low in male and female animals of the 9375-ppm treatment group and in female animals of the 1250-ppm treatment group.

From these findings, the decreased weight gain observed in male and female animals of the 9375-ppm treatment group and in female animals of the 1250-ppm treatment group was considered to be caused by decreased food efficiency as well as decreased food consumption.

A declining trend in water consumption was observed in female animals of the 9375-ppm treatment group, and particularly, it occurred at almost the same time as decreased food consumption was observed in that group.

Hematology revealed decreased red blood cell counts, decreased hematocrit values and slightly decreased hemoglobin contents in the 9375-ppm treatment group, indicating mild anemia. However, the findings could not be clearly diagnosed as anemia since reticulocyte counts in male and female animals of that group were comparable to those in male and female animals of the control group. Leukocyte classification showed an increase in the percentage of lymphocytes in male and female animals of the 9375-ppm treatment group, however it was considered to be an incidental change.

Biochemistry revealed malnutrition and changes in the parameters of the liver

possibly related to CGA-48988 in the 9375-ppm treatment group (male and female). Considering increased values of cholesterol and decreased A/G ratios in male animals and increased values of cholesterol and blood glucose and decreased values of total protein and A/G ratios due to decreased albumin levels in female animals, as well as increased liver weight, it was suggested that these findings reflected the effect of CGA-48988 on the liver. However, imbalances in the metabolism of lipid, glucose and protein were considered to reflect the effect of CGA-48988 on the liver as well as the effect of malnutrition based on the findings of increased liver weight and decreased weight gain due to decreased food consumption. Increased values of potassium were observed in male and female animals, however it is unlikely that this finding reflects the effect of CGA-48988 since the condition of serum samples may have influenced the results.

Urinalysis revealed changes in electrolyte, relative density and urine volume in the 9375-ppm treatment group (males and females), however, the values for electrolytes and relative density changed in an inverse proportion to the volume of urine, and the absolute amounts of electrolytes and organic matter eliminated during 12 hours were comparable to that of the control group. Therefore, these changes were not considered attributable to the effect of CGA-48988.

Considering the changes in organ weights and their ratio to body weight as well as the markedly decreased body weight of male and female animals in the 9375-ppm treatment group and slightly decreased body weight of female animals in the 1250-ppm treatment group, these findings suggested an evident effect of treatment with the test substance because liver weight and its ratio to body weight increased in male and female animals of the 9375-ppm treatment group. In addition, increases in the ratio of liver weight to body weight observed in male and female animals of the 1250-ppm treatment group are also considered to have been the result of treatment with the test substance. Increases in the ratio of kidney weight to body weight were observed in male and female animals of the 9375-ppm treatment group, however, it is unlikely that these findings were attributable to treatment with the test substance because kidney weight slightly decreased in female animals of that group. A statistically significant difference in the values for the other organs was observed in isolated cases, however, the effect of the test substance could not be confirmed considering the decreased weight gain observed in the high-dose groups. As described above, the effect of the test substance on the liver was supported by the biochemical findings, however, there was no histopathological change. Therefore, these liver changes are considered to be adaptive, and of no toxicological significance.

The remarkable lesions which were observed at a relatively high frequency in the histopathological examination were hyperplasia of the alveolar wall and dilation of the uterine lumen. The incidence of both of these lesions was not related to treatment with the test substance. These lesions might have been attributable to the effect of either anesthesia or the artificial effect of its withdrawal, in the case of the

former, and to a change caused by the sexual cycle of the animals, in the case of the latter. Other lesions, namely hemorrhage of the lungs, necrosis of pneumocytes and pyelonephritis were observed. However these findings were observed in isolated cases and showed no relation to treatment with the test substance. There was no histopathological change reflecting the increased liver weight observed in male and female animals of the 9375-ppm treatment group.

In conclusion, the maximum no-observed-effect level of CGA-48988 in JCL: SD rats is considered to be 250 ppm (15.61 mg/kg/day for males and 17.48 mg/kg/day for females) and the lowest-observed-adverse-effect level is considered to be 1250 ppm (79.81 mg/kg/day for males and 86.96 mg/kg/day for females).

Table 1 : Group composition

Test Group	Dose Level	n	Sex	No of animal
1	0 ppm	20	Male	1101 ~ 1120
2	50 ppm	20	Male	1201 ~ 1220
3	250 ppm	20	Male	1301 ~ 1320
4	1250 ppm	20	Male	1401 ~ 1420
5	9375 ppm	20	Male	1501 ~ 1520
6	0 ppm	20	Female	2101 ~ 2120
7	50 ppm	20	Female	2201 ~ 2220
8	250 ppm	20	Female	2301 ~ 2320
9	1250 ppm	20	Female	2401 ~ 2420
10	9375 ppm	20	Female	2501 ~ 2520

Figure 1: Number of survival rat

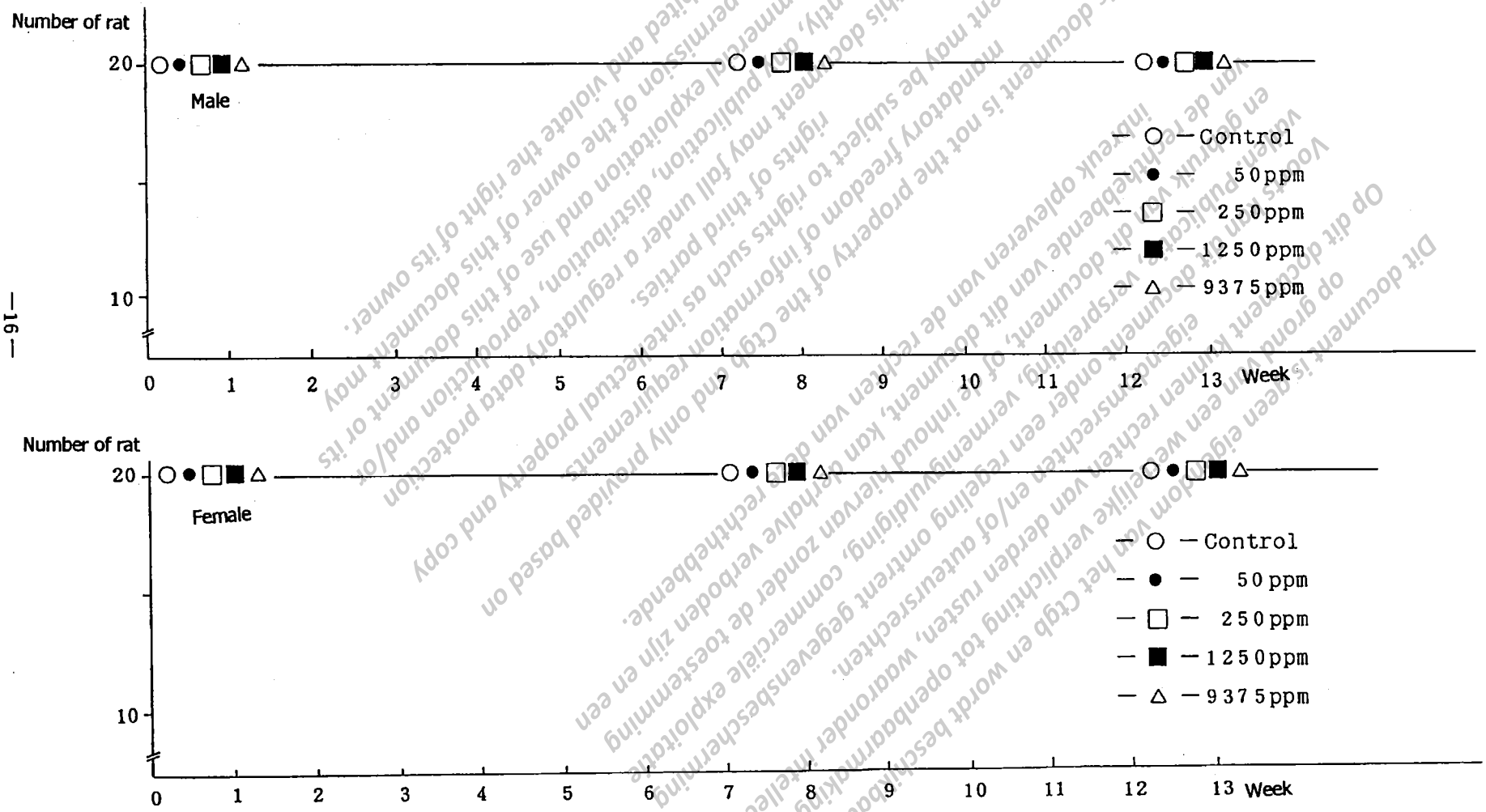


Table 2 : Number of dead rats (Male & Female)

Sex	Group	Number of death (week)													Mortality (%)
		1	2	3	4	5	6	7	8	9	10	11	12	13	
Male	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	250ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1250ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	9375ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Female	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	250ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1250ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	9375ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Figure 2: Body weight alteration (g): male

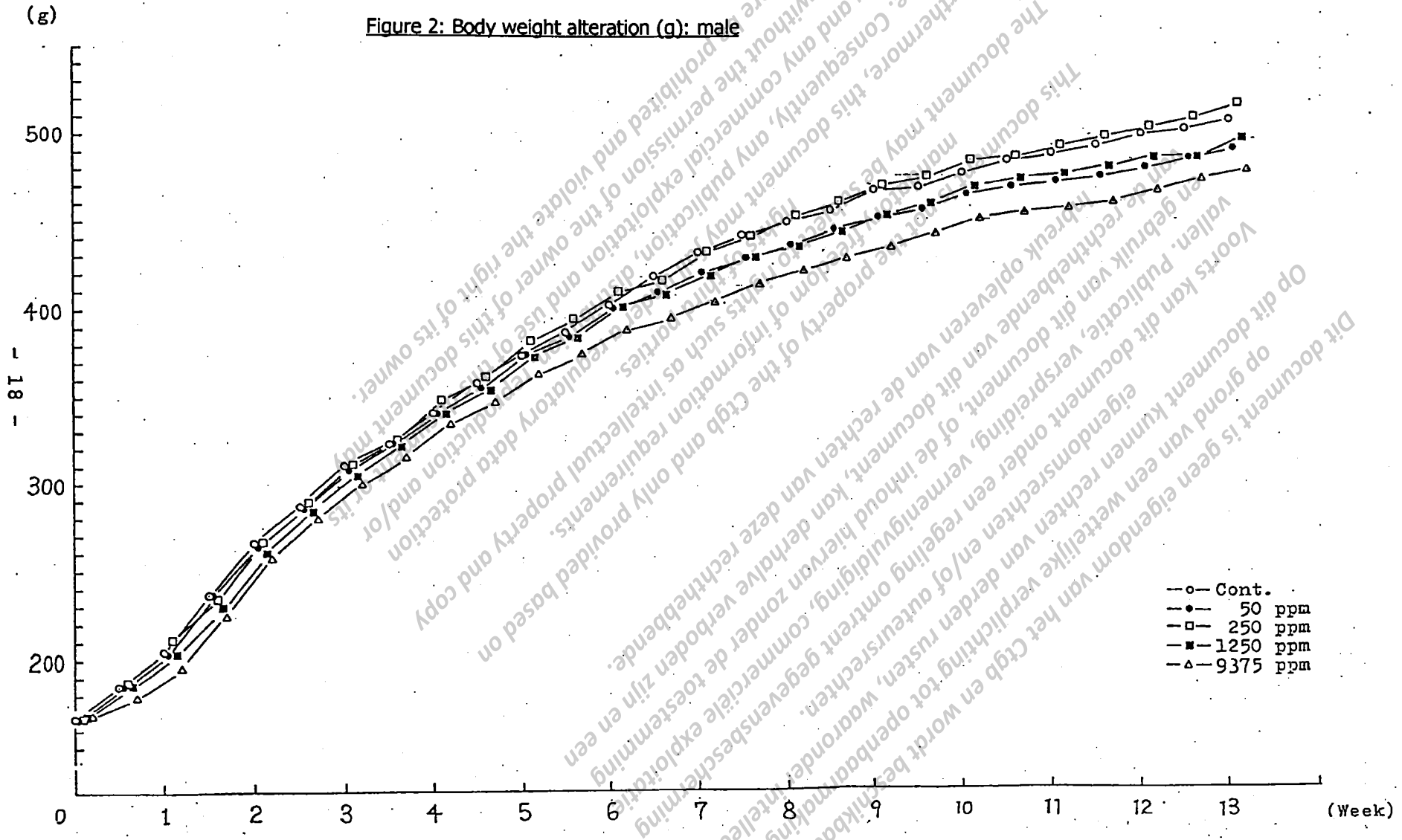


Figure 3: Body weight alteration (g): female

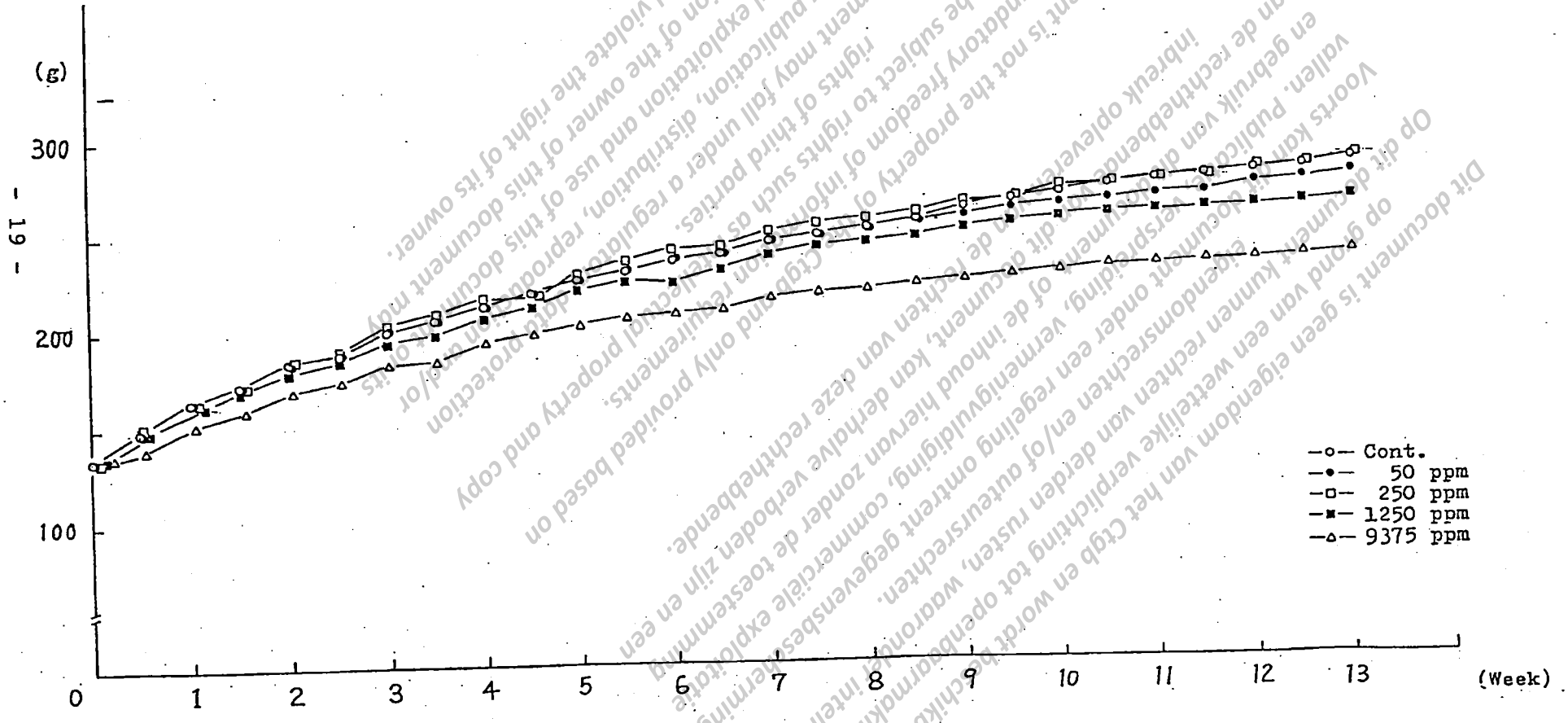


Table 3 : Changes in body weight (g): Male

Sex	Dose Level	n	No. of week for the observation													
			0		1		2		3		4		5		6	
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Male	0 ppm	20	167.40 ±6.90	186.30 ±8.27	207.30 ±7.06	238.60 ±8.88	265.70 ±11.26	286.70 ±15.32	310.90 ±17.41	323.60 ±21.42	340.90 ±23.91	358.70 ±26.50	374.40 ±28.70	387.20 ±31.15	402.30 ±32.01	419.20 ±32.74
	50 ppm	20	167.70 ±7.09	187.40 ±7.32	204.60 ±4.95	237.50 ±6.89	264.40 ±8.04	285.60 ±12.47	307.00 ±19.08	323.10 ±22.84	341.00 ±22.56	355.10 ±23.39	373.50 ±24.13	385.20 ±25.40	401.40 ±25.74	409.10 ±26.32
	250 ppm	20	167.80 ±6.45	188.10 ±7.75	212.40* ±5.17	236.60 ±5.66	267.60 ±8.09	290.30 ±12.67	312.00 ±13.27	325.60 ±17.84	349.10 ±17.41	362.40 ±18.25	382.50 ±20.10	394.70 ±22.22	409.60 ±26.38	417.90 ±26.12
	1250 ppm	20	168.60 ±7.23	185.70 ±8.97	203.90 ±6.60	230.20** ±6.77	260.50 ±9.33	284.20 ±16.06	305.50 ±18.13	321.50 ±23.47	340.40 ±27.66	354.10 ±30.31	373.00 ±34.12	384.50 ±35.93	400.75 ±38.61	407.60 ±39.39
			169.05 ±6.05	178.00** ±6.68	195.00*** ±4.44	225.40*** ±5.99	257.60* ±8.48	280.10* ±12.39	300.30* ±15.04	316.10 ±19.73	334.90 ±22.00	347.30 ±24.41	364.20 ±25.73	374.80 ±27.20	387.70 ±30.59	395.00* ±30.70

Sex	Dose Level	n	No. of week for the observation												
			7		8		9		10		11		12		13
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
Male	0 ppm	20	431.40 ±34.76	440.60 ±36.58	449.50 ±36.24	455.00 ±36.06	464.60 ±36.24	469.30 ±36.69	477.40 ±37.61	483.40 ±40.22	488.00 ±38.65	492.40 ±37.86	497.60 ±38.01	502.30 ±40.03	507.20 ±39.27
	50 ppm	20	421.00 ±26.53	428.70 ±27.71	436.60 ±28.49	444.00 ±25.57	451.30 ±31.38	456.20 ±32.22	464.10 ±34.80	468.60 ±34.90	472.10 ±36.39	474.90 ±36.31	479.80 ±34.49	485.10 ±34.97	491.00 ±37.91
	250 ppm	20	432.20 ±26.10	441.10 ±25.49	451.80 ±29.00	460.20 ±26.74	469.90 ±28.36	474.10 ±29.06	484.10 ±29.99	486.70 ±31.13	492.00 ±30.80	496.70 ±31.98	503.20 ±33.06	508.70 ±32.32	516.40 ±33.50
	1250 ppm	20	419.00 ±41.18	428.20 ±42.90	434.20 ±43.34	442.50 ±45.24	451.90 ±47.57	458.70* ±48.73	468.30 ±47.93	473.10* ±50.94	475.60 ±51.82	4794.0 ±51.70	485.90 ±54.13	485.60 ±50.46	495.90 ±56.07
			403.90* ±33.40	414.30* ±31.72	420.90* ±33.02	427.10* ±33.96	434.00* ±34.15	441.40* ±33.87	450.10* ±33.09	454.30* ±34.36	456.70** ±34.12	460.80** ±33.29	466.40* ±34.84	473.00* ±37.44	477.80* ±36.96

Mean±SD* P<0.05 ** P<0.01 *** P<0.001

Note: The measurement was conducted twice a week. "Pre" and "Post" in the table means first and second measurement respectively.

Table 4 : Changes in body weight (g): Femal

Sex	Dose Level	n	No. of week for the observation													
			0		1		2		3		4		5		6	
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Female	0 ppm	20	134.10 ±4.52	148.60 ±6.62	164.30 ±7.46	172.20 ±7.16	183.60 ±8.32	188.00 ±10.48	200.20 ±10.54	205.70 ±9.85	211.90 ±10.37	219.10 ±11.67	225.60 ±12.44	230.00 ±13.63	235.60 ±14.69	239.70 ±13.52
	50 ppm	20	133.90 ±5.21	149.20 ±6.91	164.60 ±9.11	173.00 ±10.06	182.80 ±12.98	189.80 ±13.07	201.60 ±14.55	205.50 ±15.81	212.60 ±16.09	219.60 ±16.13	226.10 ±18.40	231.80 ±18.07	237.00 ±19.35	239.10 ±19.61
	250 ppm	20	133.90 ±5.71	150.90 ±8.57	164.70 ±11.63	172.70 ±13.00	186.00 ±15.11	191.70 ±15.78	204.70 ±17.97	209.10 ±18.34	216.80 ±17.16	218.40 ±19.15	229.80 ±22.37	235.90 ±21.26	241.30 ±21.65	243.80 ±23.09
	1250 ppm	20	134.30 ±5.12	148.50 ±5.84	160.20 ±7.16	168.00 ±5.98	178.00* ±8.63	184.20 ±10.62	194.60 ±11.28	198.30 ±11.83	206.70 ±11.79	212.10 ±12.22	220.60 ±13.18	224.90 ±14.18	229.70 ±13.91	230.40 ±15.70
		20	135.00 ±5.60	138.20*** ±4.20	151.10*** ±5.37	158.90*** ±4.47	168.90*** ±7.09	173.50*** ±8.00	182.90*** ±9.39	182.80*** ±10.31	193.60*** ±10.89	197.40*** ±10.16	201.50*** ±10.72	205.30*** ±12.02	208.90*** ±14.65	209.80*** ±12.29

Sex	Dose Level	n	No. of week for the observation												
			7		8		9		10		11		12		13
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
Female	0 ppm	20	245.90 ±14.03	248.60 ±15.34	251.60 ±15.70	256.50 ±17.24	261.50 ±17.06	266.40 ±16.84	269.30 ±18.21	273.10 ±18.69	275.70 ±20.60	278.70 ±21.79	280.10 ±21.84	282.80 ±23.36	286.00 ±24.15
	50 ppm	20	245.80 ±19.31	248.30 ±19.95	250.60 ±19.93	254.30 ±21.61	256.90 ±21.77	260.40 ±21.38	263.90 ±22.17	266.20 ±23.23	267.10 ±23.37	268.80 ±23.41	273.10 ±24.80	276.70 ±26.26	279.00 ±26.81
	250 ppm	20	250.20 ±22.30	254.30 ±22.31	257.40 ±23.09	260.90 ±24.05	265.30 ±25.12	267.60 ±24.57	271.50 ±24.42	274.00 ±25.21	276.70 ±25.37	277.60 ±26.36	281.10 ±27.20	282.80 ±27.93	287.50 ±27.62
	1250 ppm	20	238.10 ±17.22	242.30 ±17.17	243.90 ±17.32	247.00 ±16.25	251.10 ±16.57	253.30* ±16.13	256.60* ± 15.95	258.00* ±16.30	259.70* ±16.30	260.60* ±17.51	262.00** ±18.74	263.50 ±18.07	265.30** ±18.10
	9375 ppm	20	215.20*** ±12.37	217.10*** ±13.60	219.10*** ±13.73	221.30*** ±13.66	223.80*** ±13.87	225.60*** ±13.50	228.20*** ±13.66	230.90*** ±14.19	231.30*** ±14.24	232.20*** ±14.36	233.90*** ±14.34	235.40*** ±14.45	236.30*** ±16.11

Mean±SD* P<0.05 ** P<0.01 *** P<0.001

Note: The measurement was conducted twice a week. "Pre" and "Post" in the table means first and second measurement respectively.

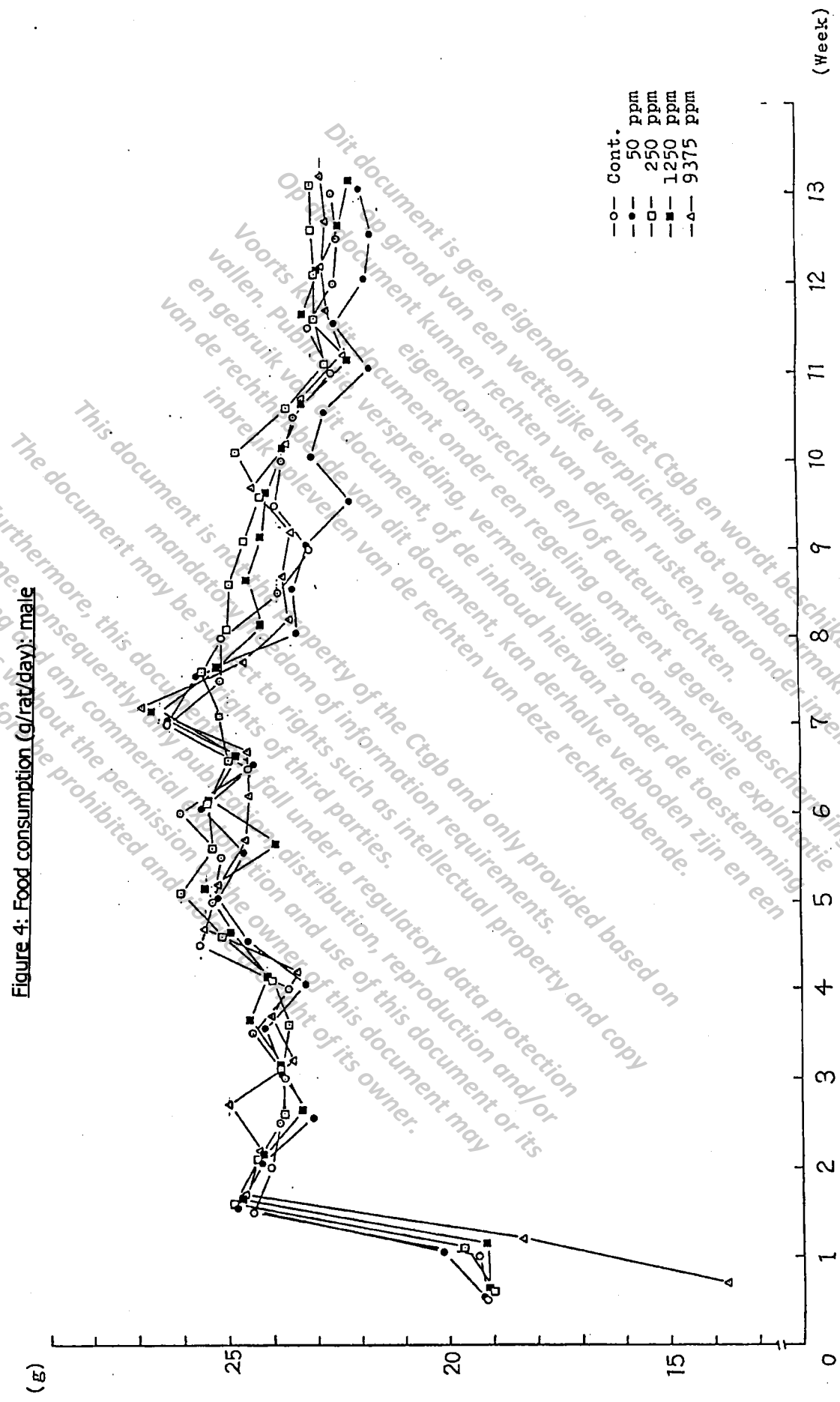


Figure 4: Food consumption (g/rat/day): male

Figure 5: Food consumption (g/rat/day): female

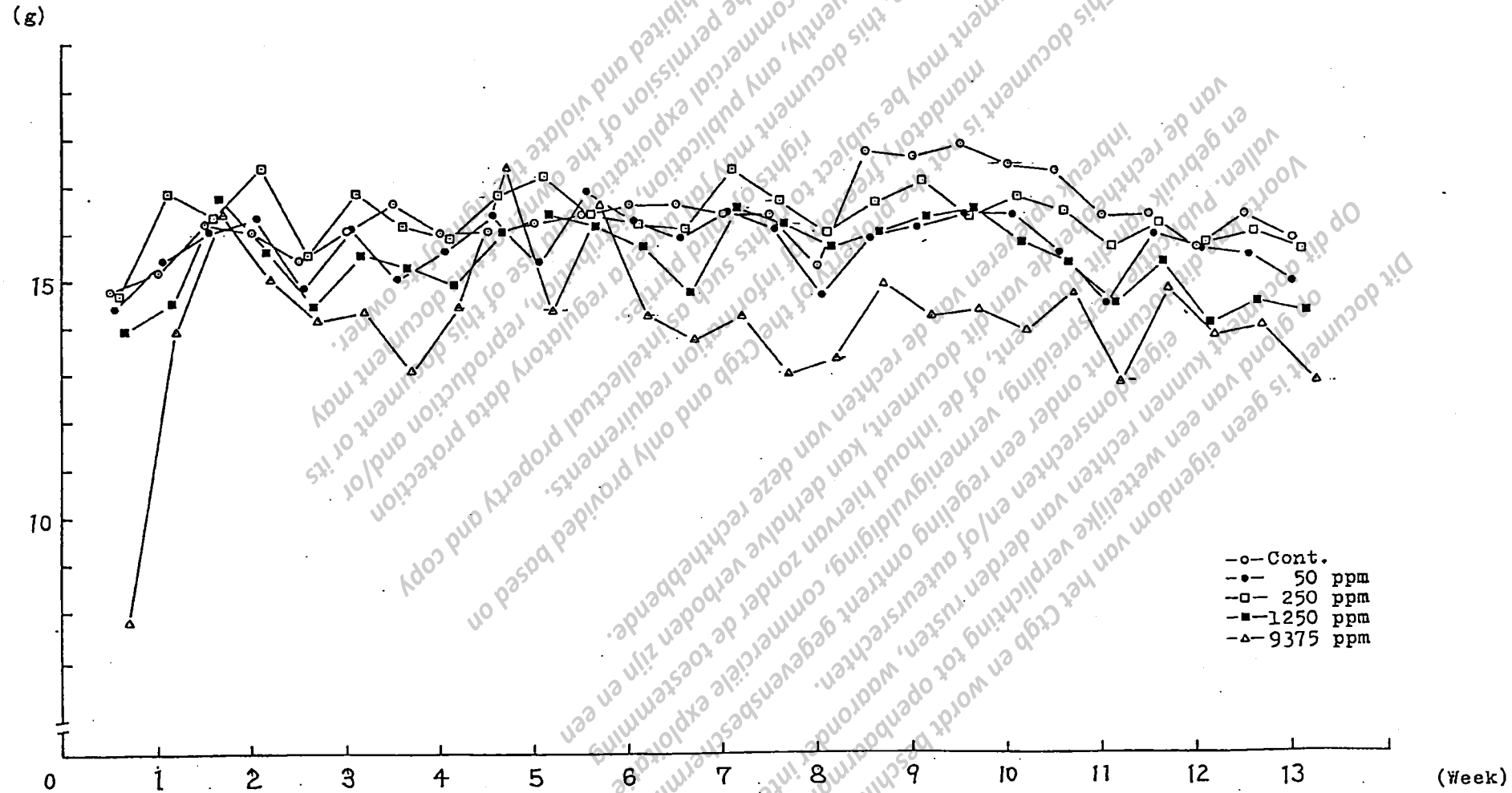


Table 5 : Food consumption (g/rat/day) : Male

Sex	Dose Level	n	No. of week for the observation												
			0	1		2		3		4		5		6	
			Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Male	0 ppm	20	19.17	19.33	24.43	24.03	23.87	23.73	24.47	23.65	25.60	25.35	25.17	26.08	24.53
	50 ppm	20	19.23	20.13	24.80	24.25	23.10	23.83	24.20	23.28	24.60	25.20	24.67	25.60	24.43
	250 ppm	20	19.00	19.68	24.90	24.38	23.77	23.85	23.67	24.03	25.13	26.08	25.37	25.48	25.00
	1250 ppm	20	19.10	19.15	24.70	24.23	23.33	23.88	24.53	24.15	24.97	25.53	23.97	25.48	24.80
	9375 ppm	20	13.73	18.33	24.67	24.33	25.00	23.58	24.03	23.48	25.50	25.23	24.60	24.53	24.57

Sex	Dose Level	n	No. of week for the observation												
			7		8		9		10		11		12		13
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Post
Male	0 ppm	20	26.33	25.17	25.13	23.87	23.43	23.93	23.78	23.50	22.60	23.13	22.55	22.50	22.60
	50 ppm	20	26.33	25.70	23.43	23.50	23.20	22.20	23.08	22.80	21.63	22.53	21.88	21.70	21.93
	250 ppm	20	25.03	25.57	25.00	24.97	24.65	24.27	24.48	23.63	22.78	23.00	23.00	23.06	23.10
	1250 ppm	20	26.65	25.23	24.25	24.57	24.28	24.10	23.78	23.30	22.28	23.30	22.98	22.43	22.20
	9375 ppm	20	26.90	24.63	23.60	23.77	23.58	24.43	23.65	23.30	22.35	22.70	22.83	22.77	22.83

Table 6 : Food consumption (g/rat/day) : Female

Sex	Dose Level	n	No. of week for the observation												
			0	1		2		3		4		5		6	
			Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Female	0 ppm	20	14.80	15.23	16.23	16.05	15.43	16.08	16.67	16.05	16.10	16.28	16.43	16.68	16.67
	50 ppm	20	14.40	15.48	16.07	16.38	14.87	16.13	15.07	15.68	16.43	15.45	16.93	16.30	15.97
	250 ppm	20	14.73	16.88	16.36	17.40	15.57	16.88	16.20	15.95	16.68	17.28	16.47	16.28	16.13
	1250 ppm	20	13.93	14.55	16.77	15.63	14.47	15.55	15.30	14.93	16.07	16.48	16.20	15.73	14.77
	9375 ppm	20	7.80	13.93	16.40	15.05	14.17	14.35	13.03	14.43	17.47	14.40	16.67	14.30	13.77

Sex	Dose Level	n	No. of week for the observation												
			7		8		9		10		11		12		13
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
Female	0 ppm	20	16.48	16.43	15.33	17.77	17.63	17.90	17.50	17.33	16.83	16.46	15.75	16.43	15.93
	50 ppm	20	16.50	16.13	14.70	15.97	16.18	16.47	16.40	15.63	14.53	16.00	15.70	15.57	15.00
	250 ppm	20	17.05	16.70	16.05	16.70	17.10	16.40	16.80	16.50	15.73	16.27	15.88	16.07	15.70
	1250 ppm	20	16.58	16.23	15.78	16.07	16.38	16.53	15.83	15.40	14.53	15.43	14.10	14.60	14.35
	9375 ppm	20	14.23	13.00	13.35	15.00	14.28	14.40	13.98	14.77	12.85	14.83	13.85	14.07	12.90

Table 7 : Test substance intake : Male

Sex	Dose Level	Parameters	No. of week for the observation													Mean TSI
			1	2	3	4	5	6	7	8	9	10	11	12	13	
Male	0 ppm	Body Weight(g)	207.30	265.70	310.90	340.90	374.40	402.30	431.40	449.50	464.60	477.40	488.00	497.60	507.20	–
		Food Consum-ption(g/day)	19.26	24.20	23.79	24.00	25.46	25.69	25.56	25.14	23.43	23.84	22.99	22.80	22.56	–
		TSI (mg/day)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		TSI (mg/kg/day)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50 ppm	Body Weight(g)	204.60	264.40	307.00	341.00	373.50	401.40	421.00	436.60	451.30	464.10	472.10	479.80	491.00	–
		Food Consum-ption(g/day)	19.74	24.49	23.51	23.67	24.94	25.20	25.51	24.40	23.34	22.70	22.13	22.16	21.83	–
		TSI (mg/day)	0.987	1.225	1.176	1.184	1.247	1.260	1.276	1.220	1.167	1.135	1.107	1.108	1.092	1.17
		TSI (mg/kg/day)	4.824	4.633	3.831	3.472	3.339	3.139	3.031	2.794	2.586	2.446	2.345	2.309	2.224	3.15
	250 ppm	Body Weight(g)	212.40	267.60	312.00	349.10	382.50	409.60	432.20	451.80	469.90	484.10	492.00	503.20	516.40	–
		Food Consum-ption(g/day)	19.39	24.60	23.81	23.87	25.67	25.43	25.01	25.24	24.79	24.39	23.14	23.00	23.09	–
		TSI (mg/day)	4.848	6.150	5.953	5.968	6.418	6.358	6.253	6.310	6.198	6.098	5.785	5.750	5.773	5.99
		TSI (mg/kg/day)	22.825	22.982	19.080	17.095	16.779	15.522	14.468	13.966	13.190	12.597	11.758	11.427	11.179	15.61
	1250 ppm	Body Weight(g)	203.90	260.50	305.50	340.40	373.00	400.75	419.00	434.20	451.90	468.30	475.60	485.90	495.90	–
		Food Consum-ption(g/day)	19.13	24.43	23.64	24.31	25.29	24.83	25.86	24.67	24.40	23.91	22.71	23.11	22.30	–
		TSI (mg/day)	23.913	30.538	29.550	30.388	31.613	31.038	32.325	30.838	30.500	29.888	28.388	28.888	27.875	29.67
		TSI (mg/kg/day)	117.278	117.228	96.727	89.271	84.753	77.450	77.148	71.023	67.493	63.822	56.689	59.453	56.211	79.81
	9375 ppm	Body Weight(g)	195.50	257.60	300.30	334.90	364.20	387.70	403.90	420.90	434.00	450.10	456.70	466.40	477.80	–
		Food Consum-ption(g/day)	16.36	24.47	24.19	23.71	25.34	24.56	25.90	24.04	23.66	23.99	22.73	22.77	22.80	–
		TSI (mg/day)	153.375	229.406	226.781	222.281	237.563	230.250	242.813	225.375	221.813	224.906	213.094	213.469	213.750	219.61
		TSI (mg/kg/day)	784.527	890.551	755.181	663.723	652.287	593.887	601.171	535.460	511.090	499.680	466.595	457.695	447.363	604.55

Table 8 : Test substance intake : Female

Sex	Dose Level	Parameters	No. of week for the observation													Mean TSI
			1	2	3	4	5	6	7	8	9	10	11	12	13	
Female	0 ppm	Body Weight(g)	164.30	183.60	200.20	211.90	225.60	235.60	245.90	251.60	261.50	269.30	275.70	280.10	286.00	–
		Food Consum-ption(g/day)	15.04	16.13	15.80	16.31	16.20	16.57	16.56	15.80	17.69	17.67	16.83	16.06	16.14	–
		TSI (mg/day)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		TSI (mg/kg/day)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	50 ppm	Body Weight(g)	164.60	182.80	201.60	212.60	226.10	237.00	245.80	250.60	256.90	263.90	267.10	273.10	279.00	–
		Food Consum-ption(g/day)	15.01	16.24	15.59	15.69	15.87	16.57	16.27	15.34	16.09	16.43	15.00	15.83	15.24	–
		TSI (mg/day)	0.751	0.812	0.780	0.784	0.794	0.829	0.814	0.767	0.805	0.822	0.750	0.792	0.762	0.79
		TSI (mg/kg/day)	4.563	4.442	3.869	3.688	3.512	3.498	3.312	3.061	3.134	3.115	2.808	2.900	2.731	3.43
	250 ppm	Body Weight(g)	164.70	186.00	204.70	216.80	229.80	241.30	250.20	257.40	265.30	271.50	276.70	281.10	287.50	–
		Food Consum-ption(g/day)	15.96	16.93	16.31	16.06	17.00	16.36	16.66	16.33	16.93	16.63	16.06	16.04	15.86	–
		TSI (mg/day)	3.990	4.233	4.078	4.015	4.250	4.090	4.165	4.083	4.233	4.158	4.015	4.010	3.965	4.10
		TSI (mg/kg/day)	24.226	22.758	19.922	18.519	18.494	16.950	16.647	15.862	15.956	15.315	14.510	14.265	13.791	17.48
	1250 ppm	Body Weight(g)	160.20	178.00	194.60	206.70	220.60	229.70	238.10	243.90	251.10	256.60	259.70	262.00	265.30	–
		Food Consum-ption (g/day)	14.29	16.11	15.80	15.09	16.30	15.93	15.80	15.97	16.24	16.13	14.90	14.67	14.46	–
		TSI (mg/day)	17.863	20.138	19.750	18.863	20.375	19.913	19.750	19.963	20.300	20.163	18.625	18.338	18.075	19.39
		TSI (mg/kg/day)	111.504	113.135	101.490	91.258	92.362	86.691	82.948	81.849	80.844	78.578	71.717	69.992	68.130	86.96
	9375 ppm	Body Weight(g)	151.10	168.90	182.90	193.60	201.50	208.90	215.20	219.10	223.80	228.20	231.30	233.90	236.30	–
		Food Consum-ption(g/day)	11.30	15.63	14.27	13.83	15.71	15.31	14.03	13.20	14.59	14.16	13.41	14.27	13.40	–
		TSI (mg/day)	105.938	146.531	133.781	129.656	147.281	143.531	131.531	123.750	136.781	132.750	125.719	133.781	125.625	132.05
		TSI (mg/kg/day)	701.112	867.561	731.443	669.711	730.923	687.080	611.204	564.811	611.175	581.727	543.532	571.958	531.634	646.45

Table 9 : Mean Test Substance Intake

Dose Level	Test Substance intake (mg/kg/day)		Mean TSI Combined both sexes (mg/kg/day)
	Male	Female	
0 ppm	—	—	—
50 ppm	3.15	3.43	3.29
250 ppm	15.61	17.48	16.55
1250 ppm	79.81	86.96	83.39
9375 ppm	604.55	646.45	625.55

Table 10 : Food Efficiency

Week	Sex		Male					Female				
	Parameters		0 ppm	50 ppm	250 ppm	1250 ppm	9375 ppm	0 ppm	50 ppm	250 ppm	1250 ppm	9375 ppm
5	Body weight at the start	g	167.40	167.70	167.80	168.60	169.05	134.10	133.90	133.90	134.30	135.00
	Body weight at the 5th week	g	374.40	373.50	382.50	373.00	364.20	225.60	226.10	229.80	220.60	201.50
	Increased Body weight	g	207.00	205.80	214.70	204.40	195.15	91.50	92.20	95.90	86.30	66.50
	Increased Body weight	%	123.66	122.72	127.95	121.23	115.44	68.23	68.86	71.62	64.26	49.26
	Food consumption for 5 weeks	g	816.90	814.50	821.40	817.60	798.50	556.40	548.70	575.80	543.10	495.20
	Mean daily food consumption	g	23.34	23.27	23.47	23.36	22.81	15.90	15.68	16.45	15.52	14.15
	Food Efficiency	%	25.34	25.27	26.14	25.00	24.44	16.44	16.80	16.66	15.89	13.43
13	Body weight at the start (g)	g	167.40	167.70	167.80	168.60	169.05	134.10	133.90	133.90	134.30	135.00
	Body weight at the 13th week	g	507.20	491.00	516.40	495.90	477.80	286.00	279.00	287.50	265.30	236.30
	Increased Body weight	g	339.80	323.30	348.60	327.30	308.75	151.90	145.10	153.60	131.00	101.30
	Increased Body weight	%	202.99	192.78	207.75	194.13	182.64	113.27	108.36	114.71	97.54	75.04
	Food consumption for 13 weeks	g	2161.00	2125.40	2180.00	2160.20	2131.60	1489.60	1435.90	1491.80	1411.80	1281.80
	Mean daily food consumption	g	23.75	23.36	23.96	23.74	23.42	16.37	15.78	16.39	15.51	14.09
	Food Efficiency	%	15.72	15.21	15.99	15.15	14.48	10.20	10.11	10.30	9.28	7.90

Figure 6: Water consumption (mL/rat/day): male

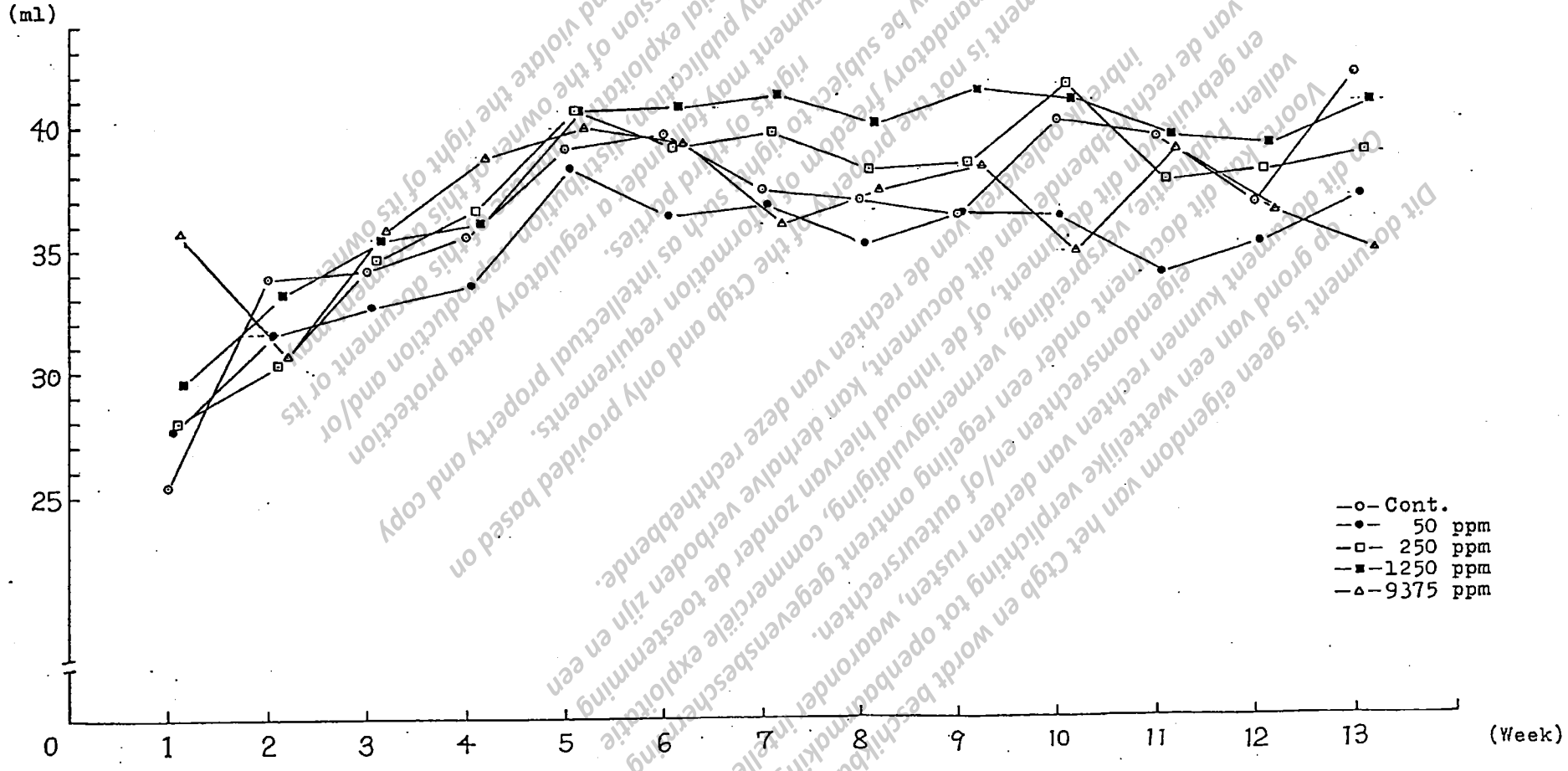


Figure 7: Water consumption (ml/rat/day): female

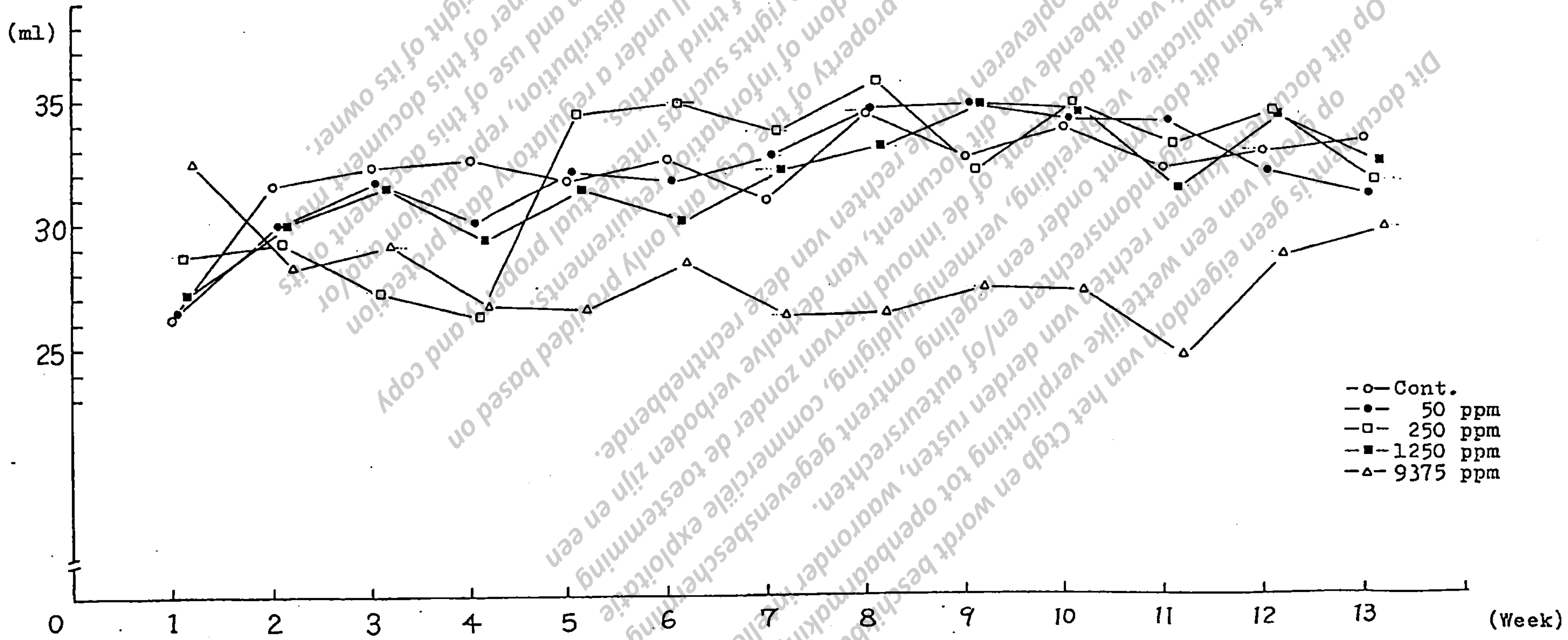


Table 11 : Water consumption (mL/rat/day) : Male

Sex	Dose Level	n	No. of week for observation												
			1	2	3	4	5	6	7	8	9	10	11	12	13
Male	0 ppm	20	25.40	33.90	34.20	35.60	39.10	39.80	37.50	37.00	36.50	40.20	39.60	37.00	42.20
	50 ppm	20	27.80	31.60	32.70	33.60	38.40	36.50	36.90	35.30	36.60	36.50	34.00	35.40	37.30
	250 ppm	20	28.00	30.30	34.70	36.70	40.70	39.20	39.80	38.30	38.60	41.70	37.90	38.20	39.00
	1250 ppm	20	29.60	33.20	35.50	36.20	40.70	41.00	41.20	40.30	41.40	41.10	39.80	39.40	41.20
	9375 ppm	20	35.80	30.70	35.90	38.80	40.00	39.40	36.10	37.50	38.40	35.00	39.04	36.60	35.00

Table 12 : Water consumption (mL/rat/day) : Female

Sex	Dose Level	n	No. of week for the observation												
			1	2	3	4	5	6	7	8	9	10	11	12	13
Female	0 ppm	20	26.20	31.60	32.30	32.60	31.80	32.70	31.00	34.40	32.70	33.90	32.30	33.00	33.30
	50 ppm	20	26.40	30.00	31.70	30.10	32.20	31.70	32.80	34.80	34.90	34.30	34.20	32.10	31.20
	250 ppm	20	28.70	29.20	27.30	26.30	34.50	34.80	33.80	35.80	32.20	35.00	33.10	34.60	31.70
	1250 ppm	20	27.20	30.00	31.40	29.40	31.30	30.10	32.10	33.10	34.90	34.60	31.40	34.50	32.50
	9375 ppm	20	32.40	28.30	29.10	26.70	26.50	28.40	26.30	26.40	27.50	27.40	24.80	28.70	29.80

Table 13－1 : Hematological findings

Sex	Dose Level	n	RBC $10^4/mm^3$	Hct %	Hb g/dL	Plt $10^4/mm^3$	WBC $10^2/mm^3$	Differential WBC count %						Retic ‰
								Lymp.	Eosi	Mono	Baso	Stab	Seg	
Male	0 ppm	20	832.85 ±74.73	49.25 ± 1.97	16.44 ± 0.76	107.20 ±23.44	141.30 ±19.89	75.65 ± 9.08	2.95 ± 1.73	1.10 ± 1.25	0.20 ± 0.41	0.05 ± 0.22	20.05 ± 8.85	2.09 ± 1.20
	50 ppm	20	848.45 ±76.03	48.80 ± 1.61	16.07 ± 0.63	105.90 ±20.67	140.65 ±17.00	72.25 ± 8.17	3.50 ± 2.28	1.15 ± 1.57	0.55 ± 1.05	0.15 ± 0.37	22.40 ± 7.82	2.15 ± 1.77
	250 ppm	20	838.35 ±72.49	48.90 ± 2.71	16.07 ± 0.81	106.75 ±19.83	151.05 ±31.77	71.30 ± 7.85	3.70 ± 2.27	1.00 ± 1.34	0.50 ± 0.83	0.10 ± 0.31	23.40 ± 6.84	2.18 ± 1.31
	1250 ppm	20	839.55 ±56.12	48.60 ± 2.50	16.17 ± 0.83	104.70 ±26.98	142.40 ±26.74	78.75 ± 7.09	2.90 ± 2.20	1.00 ± 1.08	0.35 ± 0.59	0.20 ± 0.41	16.80 ± 5.90	1.87 ± 1.12
	9375 ppm	20	806.80 ±49.76	47.80* ± 2.24	15.97* ± 0.65	101.35 ±23.66	148.15 ±21.17	80.35* ± 4.58	2.15 ± 1.53	1.00 ± 1.41	0.20 ± 0.52	0.10 ± 0.31	16.20 ± 3.69	2.09 ± 1.82
Female	0 ppm	20	806.50 ±47.06	47.10 ± 2.65	16.36 ± 1.00	102.35 ±20.09	131.80 ±23.00	77.55 ± 6.13	2.80 ± 2.12	1.50 ± 1.28	0.20 ± 0.52	0.30 ± 0.47	17.65 ± 5.89	2.15 ± 2.87
	50 ppm	20	792.60 ±81.00	46.00 ± 2.81	16.01 ± 0.82	105.40 ±20.01	118.55 ±27.00	76.90 ± 7.30	2.75 ± 1.86	1.90 ± 1.62	0.35 ± 0.59	0.50 ± 0.95	17.60 ± 5.58	1.97 ± 2.44
	250 ppm	20	803.95 ±107.41	46.55 ± 2.46	16.11 ± 1.07	102.55 ±27.33	124.15 ±23.67	78.45 ± 8.68	2.60 ± 2.44	1.45 ± 1.47	0.65 ± 1.09	0.25 ± 0.44	16.60 ± 7.11	2.25 ± 2.56
	1250 ppm	20	799.00 ±82.72	46.25 ± 1.94	16.03 ± 1.17	99.15 ±22.30	123.80 ±19.57	80.45 ± 6.75	2.25 ± 1.71	1.20 ± 1.20	0.05 ± 0.22	0.10 ± 0.31	15.95 ± 5.99	1.98 ± 2.33
	9375 ppm	20	769.65* ±56.27	45.50* ± 2.19	15.80 ± 0.84	91.85 ±22.15	118.80 ±20.17	81.30* ± 4.77	1.85 ± 1.79	1.30 ± 1.53	0.30 ± 0.47	0.20 ± 0.62	15.05 ± 5.20	2.10 ± 3.06

Mean ± SD * $p < 0.05$

Table 13－2 : Hematological findings

Sex	Dose Level	n	MCH (mean corpuscular hemoglobin) Pg	MCV (mean corpuscular volume) μm^3	MCHC (mean corpuscular hemoglobin concentration) %
Male	0 ppm	20	19.88 ± 1.76	59.48 ± 4.69	33.41 ± 1.35
	50 ppm	20	19.03 ± 1.26	57.87 ± 4.38	32.93 ± 1.11
	250 ppm	20	19.25 ± 1.29	58.56 ± 3.58	32.92 ± 1.80
	1250 ppm	20	19.29 ± 0.94	58.06 ± 3.99	33.33 ± 2.15
	9375 ppm	20	19.83 ± 1.03	59.36 ± 2.89	33.45 ± 1.52
Female	0 ppm	20	20.32 ±11.15	58.54 ± 3.93	34.75 ± 1.62
	50 ppm	20	20.33 ± 1.51	58.34 ± 3.71	34.87 ± 1.62
	250 ppm	20	20.27 ± 2.01	58.76 ± 7.41	34.65 ± 2.28
	1250 ppm	20	20.17 ± 1.64	58.34 ± 5.06	34.05 ± 3.33
	9375 ppm	20	20.58 ± 1.20	59.31 ± 3.58	34.72 ± 1.19

Mean±SD

Table 14 : Biochemical findings

Sex	Dose Level	n	GOT (KARMEN unit)	GPT (KARMEN unit)	Alkaline phosphatase K.A.unit	A/G ratio	Blood glucose mg/dL	Total protein g/dL	Blood urea nitrogen mg/dL	Chole-sterol mg/dL	Sodium (mEg/L)	Potassium (mEg/L)	Chlor. (mEg/L)	Creatinine mg/dL	Albumin mg/dL
Male	0 ppm	20	111.43 ±13.90	37.98 ± 2.86	25.10 ± 5.47	1.03 ± 0.23	142.94 ±19.29	6.56 ± 0.17	17.56 ± 1.53	66.67 ±12.42	145.15 ± 1.81	5.11 ± 0.50	101.55 ± 3.94	0.91 ± 0.09	3.88 ± 0.18
	50 ppm	20	104.45 ±11.29	37.63 ± 2.91	25.96 ± 4.64	1.09 ± 0.21	143.03 ±17.74	6.54 ± 0.39	16.85 ± 2.11	62.25 ± 8.10	144.20 ± 1.96	5.01 ± 0.55	101.60 ± 4.75	0.86 ± 0.10	3.89 ± 0.16
	250 ppm	20	104.85 ±16.40	38.05 ± 2.19	25.00 ± 7.98	1.06 ± 0.26	151.30 ±12.85	6.62 ± 0.27	16.98 ± 2.49	68.27 ±11.59	144.35 ± 1.93	5.30 ± 0.42	100.00 ± 4.60	0.88 ± 0.08	0.96 ± 0.14
	1250 ppm	20	101.75 ±18.88	39.80 ± 4.64	25.40 ± 7.43	0.98 ± 0.21	146.58 ±15.56	6.55 ± 0.28	16.44 ± 2.12	62.58 ± 9.85	144.75 ± 1.41	5.37 ± 0.56	99.50 ± 3.72	0.96 ± 0.12	3.98 ± 0.21
	9375 ppm	20	103.55 ±16.03	35.55 ± 4.65	22.18 ± 5.75	0.90* ± 0.16	147.65 ±16.96	6.41 ± 0.34	17.07 ± 1.85	77.00* ±13.95	144.10 ± 2.25	5.43* ± 0.45	101.60 ± 4.76	0.93 ± 0.09	3.77 ± 0.29
Female	0 ppm	20	109.48 ±14.90	37.90 ± 6.04	17.17 ± 6.77	1.35 ± 0.20	112.33 ± 8.83	7.00 ± 0.52	18.05 ± 2.63	90.84 ±20.20	144.40 ± 1.82	5.59 ± 0.48	99.45 ± 2.26	0.93 ± 0.10	4.06 ± 0.29
	50 ppm	20	102.43 ±21.63	37.33 ±11.66	14.48 ± 4.23	1.37 ± 0.12	117.04 ± 9.07	6.73 ± 0.39	19.65 ± 3.76	89.77 ±19.49	144.15 ± 0.99	5.72 ± 0.47	95.55 ± 2.82	0.95 ± 0.10	4.03 ± 0.23
	250 ppm	20	101.00 ±15.11	35.88 ± 2.78	15.98 ± 5.11	1.42 ± 0.21	118.46 ±10.42	6.85 ± 0.37	16.20 ± 3.33	86.15 ±13.70	144.30 ± 1.38	5.69 ± 0.51	100.10 ± 3.71	0.99 ± 0.16	4.05 ± 0.22
	1250 ppm	20	103.98 ±22.36	39.55 ±11.10	15.72 ± 5.90	1.31 ± 0.25	117.12 ± 9.55	6.76 ± 0.28	16.76 ± 3.23	88.48 ±11.50	144.90 ± 1.52	5.75 ± 0.81	100.00 ± 3.39	0.89 ± 0.15	4.03 ± 0.25
	9375 ppm	20	101.03 ±14.09	35.88 ± 4.52	13.72 ± 5.41	1.20* ± 0.21	119.09* ± 9.40	6.71* ± 0.32	17.30 ± 2.22	107.22* ±22.98	143.80 ± 2.33	5.39 ± 1.19	99.45 ± 3.90	1.00 ± 0.18	3.89* ± 0.23

Mean±SD* P<0.05

Table 15 : Urinalysis findings

Sex	Dose Level	n	Fresh blood reaction			Ketone		Body glucose		Protein			pH			Urobili-nogen	Bilirubin		Sodium	Potassium	SG	Urine Volume	RBC				WBC			Squamous cells			Crystal		Bacteria	
			−	±	+	−	+	−	+	−	±	+	6	7	8	0.1	−	+	mEg/L				0	0∼1	1∼5	5∼20	0	0∼1	1∼5	0	0∼1	1∼5	−	+	−	+
Male	0 ppm	20	20	0	0	20	0	20	0	0	15	5	18	2	0	20	20	0	110.00 ±44.40	314.80 ±92.35	1.072 ±0.01	4.56 ±1.35	14	6	0	0	11	5	4	11	7	2	0	20	20	0
	50 ppm	20	20	0	0	20	0	20	0	0	15	5	13	6	1	20	20	0	130.00 ±39.42	340.40 ±106.87	1.068 ±0.02	5.32 ±1.68	12	5	3	0	12	6	2	14	5	1	0	20	20	0
	250 ppm	20	20	0	0	20	0	20	0	0	17	3	13	7	0	20	20	0	121.20 ±45.42	330.40 ±92.04	1.068 ±0.02	5.03 ±2.28	14	5	1	0	12	5	3	13	5	2	0	20	20	0
	1250 ppm	20	20	0	0	20	0	20	0	0	18	2	16	4	0	20	20	0	100.20 ±34.47	331.40 ±166.78	1.069 ±0.01	5.17 ±2.18	15	5	0	0	16	4	0	14	6	0	0	20	20	0
	9375 ppm	20	20	0	0	20	0	20	0	0	17	3	11	9	0	20	20	0	81.60* ±25.54	269.80 ±89.02	1.061* ±0.02	6.58* ±3.23	19	1	0	0	17	3	0	16	4	0	0	20	20	0
Female	0 ppm	20	20	0	0	20	0	20	0	0	17	3	18	1	1	20	20	0	116.20 ±44.17	222.20 ±38.51	1.064 ±0.01	3.05 ±0.98	13	7	0	0	12	8	0	9	7	4	0	20	20	0
	50 ppm	20	20	0	0	20	0	20	0	0	13	7	20	0	0	20	20	0	106.80 ±29.51	233.20 ±70.24	1.063 ±0.02	2.41 ±1.36	9	11	0	0	11	9	0	14	6	0	0	20	20	0
	250 ppm	20	19	0	1	20	0	20	0	0	15	5	19	1	0	20	20	0	100.20 ±31.46	234.00 ±90.59	1.062 ±0.02	2.60 ±1.56	10	8	2	0	17	2	1	14	4	2	0	20	20	0
	1250 ppm	20	20	0	0	20	0	20	0	0	13	7	19	1	0	20	20	0	113.60 ±43.98	264.00 ±89.57	1.063 ±0.01	2.66 ±1.39	10	9	1	0	17	3	0	15	3	2	0	20	20	0
	9375 ppm	20	18	0	2	20	0	20	0	0	12	8	20	0	0	20	20	0	145.20 ±50.38	297.80** ±106.17	1.066 ±0.01	2.34 ±1.98	12	4	4	0	11	8	1	10	6	4	0	20	20	0

Mean±SD* P<0.1 ** P<0.01

Table 16 : Organ Weight

Sex	Dose Level	n	Brain g	Heart g	Lung g	Liver g	Spleen g	Kidneys g R	Kidneys g L	Testes g R	Testes g L	Prostate mg	Adrenals mg R	Adrenals mg L	Thymus mg	Thyroid mg	Pituitary mg	Pancreas g	Seminal Vesicle g
Male	0 ppm	20	2.01 ±0.10	1.33 ±0.14	1.53 ±0.15	12.40 ±1.31	0.81 ±0.15	1.48 ±0.14	1.46 ±0.13	1.85 ±0.15	1.87 ±0.11	530.05 ±159.43	26.25 ±6.98	26.20 ±4.47	295.00 ±95.76	21.30 ± 4.32	13.15 ±2.54	0.60 ±0.17	0.73 ±0.15
	50 ppm	20	2.04 ±0.10	1.34 ±0.14	1.48 ±0.15	12.32 ±1.55	0.77 ±0.11	1.45 ±0.15	1.45 ±0.18	1.86 ±0.16	1.84 ±0.13	556.95 ±156.00	26.20 ±5.01	26.55 ±6.27	255.45 ±73.86	18.95 ± 3.86	13.70 ±1.78	0.57 ±0.15	0.76 ±0.17
	250 ppm	20	2.02 ±0.07	1.37 ±0.11	1.50 ±0.10	13.26 ±1.65	0.89 ±0.12	1.51 ±0.15	1.48 ±0.16	1.82 ±0.18	1.87 ±0.12	515.40 ±102.71	26.25 ±4.08	28.90 ±4.67	305.20 ±66.66	18.85 ± 5.66	14.50 ±3.30	0.56 ±0.09	0.71 ±0.13
	1250 ppm	20	2.04 ±0.12	1.40 ±0.21	* 1.42 ±0.17	13.18 ±1.56	0.79 ±0.09	1.50 ±0.15	1.47 ±0.18	1.83 ±0.15	1.83 ±0.14	530.50 ±109.84	24.35 ±2.96	27.85 ±4.48	242.30 ±94.46	19.10 ± 3.81	12.85 ±2.70	0.56 ±0.08	0.83 ±0.24
	9375 ppm	20	1.99 ±0.10	1.29 ±0.17	* 1.43 ±0.13	*** 15.59 ±2.10	0.81 ±0.14	1.52 ±0.15	1.54 ±0.15	1.83 ±0.19	1.88 ±0.16	564.15 ±148.54	25.35 ±5.69	28.35 ±4.34	265.60 ±99.71	19.55 ± 4.62	12.80 ±2.63	0.58 ±0.14	0.80 ±0.17

Sex	Dose Level	n	Brain g	Heart g	Lung g	Liver g	Spleen g	Kidneys g R	Kidneys g L	Uterus g	Ovaries mg R	Ovaries mg L	Adrenals mg R	Adrenals mg L	Thymus mg	Thyroid mg	Pituitary mg	Pancreas g
Female	0 ppm	20	1.89 ±0.08	0.81 ±0.08	1.15 ±0.06	6.99 ±0.84	0.56 ±0.07	0.89 ±0.09	0.88 ±0.08	0.51 ±0.14	41.10 ±10.13	40.35 ± 8.27	30.55 ± 3.72	30.90 ± 5.36	199.75 ±41.69	15.75 ± 2.59	14.70 ± 2.27	0.40 ± 0.06
	50 ppm	20	1.87 ±0.09	0.79 ±0.08	1.09 ±0.11	7.02 ±0.83	0.55 ±0.08	0.91 ±0.16	0.88 ±0.16	0.53 ±0.07	41.25 ± 9.53	41.40 ± 8.49	31.55 ± 5.29	31.70 ± 6.78	197.00 ±39.46	16.40 ± 2.87	14.75 ± 2.24	0.42 ± 0.06
	250 ppm	20	1.90 ±0.10	0.81 ±0.09	1.10 ±0.10	7.24 ±0.79	0.52 ±0.07	0.92 ±0.11	0.91 ±0.10	0.49 ±0.13	42.45 ± 8.21	40.75 ± 9.52	29.10 ± 5.00	32.30 ± 5.97	209.45 ±54.41	15.85 ± 3.79	14.50 ± 2.26	0.44 ± 0.07
	1250 ppm	20	1.86 ±0.08	* 0.76 ±0.06	* 1.08 ±0.09	8.08 ±0.64	0.52 ±0.07	* 0.82 ±0.10	* 0.83 ±0.05	0.49 ±0.11	40.50 ± 9.22	40.20 ± 7.15	30.15 ± 4.25	28.55 ± 6.35	189.25 ±45.40	15.15 ± 4.44	14.70 ± 2.45	0.40 ± 0.06
	9375 ppm	20	* 1.82 ±0.09	** 0.74 ±0.07	*** 1.04 ±0.09	*** 8.76 ±0.61	* 0.50 ±0.08	* 0.83 ±0.08	* 0.83 ±0.14	0.54	* 34.50 ± 6.64	35.50 ± 8.11	30.25 ± 4.46	27.95 ± 5.33	190.30 ±56.74	14.50 ± 3.02	13.80 ± 2.75	0.37 ± 0.05

Mean±SD* P<0.05 *** P<0.001

Table 17 : Ratio of organ weight to body weight (%)

Sex	Dose Level	n	Brain g%	Heart g%	Lung g%	Liver g%	Spleen g%	Kidneys g% R	Kidneys g% L	Testes g% R	Testes g% L	Prostate mg%	Adrenals mg% R	Adrenals mg% L	Thymus mg%	Thyroid mg%	Pituitary mg%	Pancreas g%	Seminal Vesicle g%
Male	0 ppm	20	0.40 ±0.03	0.26 ±0.02	0.30 ±0.02	2.44 ±0.16	0.16 ±0.03	0.29 ±0.03	0.29 ±0.02	0.37 ±0.04	0.37 ±0.03	105.18 ±33.55	5.21 ±1.46	5.20 ±1.03	58.37 ±19.32	4.22 ±0.92	2.60 ±0.50	0.12 ±0.03	0.14 ±0.03
	50 ppm	20	0.42 ±0.04	0.28 ±0.03	0.30 ±0.03	2.51 ±0.24	0.16 ±0.02	0.30 ±0.02	0.30 ±0.03	0.38 ±0.04	0.38 ±0.04	114.50 ±34.70	5.37 ±1.14	5.43 ±1.35	52.34 ±15.27	3.87 ±0.79	2.80 ±0.35	0.12 ±0.03	0.15 ±0.03
	250 ppm	20	0.39 ±0.03	0.27 ±0.02	0.29 ±0.02	2.56 ±0.22	0.17 ±0.02	0.29 ±0.03	0.29 ±0.03	0.35 ±0.05	0.36 ±0.03	99.98 ±19.43	5.08 ±0.69	5.61 ±0.91	58.99 ±12.04	3.67 ±1.15	2.81 ±0.62	0.11 ±0.01	0.14 ±0.03
	1250 ppm	20	0.42 ±0.04	0.28 ±0.05	0.29 ±0.02	*** 2.66 ±0.16	0.16 ±0.02	0.31 ±0.02	0.30 ±0.03	0.37 ±0.04	0.37 ±0.04	108.13 ±24.89	4.97 ±0.78	5.56 ±0.93	49.47 ±19.39	3.85 ±0.64	2.59 ±0.46	0.12 ±0.02	0.17 ±0.05
	9375 ppm	20	0.42 ±0.04	0.27 ±0.03	0.30 ±0.02	*** 3.26 ±0.29	0.17 ±0.03	** 0.32 ±0.03	*** 0.32 ±0.03	0.38 ±0.04	* 0.40 ±0.04	118.84 ±33.07	5.31 ±1.16	* 5.95 ±0.91	55.83 ±20.66	4.11 ±0.99	2.68 ±0.48	0.12 ±0.03	* 0.17 ±0.04

Sex	Dose Level	n	Brain g%	Heart g%	Lung g%	Liver g%	Spleen g%	Kidneys g% R	Kidneys g% L	Uterus g%	Ovaries mg% R	Ovaries mg% L	Adrenals mg% R	Adrenals mg% L	Thymus mg%	Thyroid mg%	Pituitary mg%	Pancreas g%
Female	0 ppm	20	0.67 ±0.06	0.29 ±0.02	0.40 ±0.03	2.44 ±0.16	0.20 ±0.03	0.31 ±0.03	0.31 ±0.03	0.18 ±0.05	14.41 ±3.65	14.18 ±3.19	10.74 ±1.45	10.85 ±1.97	69.55 ±11.32	5.51 ±0.82	5.14 ±0.70	0.14 ±0.02
	50 ppm	20	0.68 ±0.06	0.28 ±0.03	0.39 ±0.04	2.52 ±0.24	0.20 ±0.03	0.33 ±0.05	0.31 ±0.05	0.19 ±0.03	14.95 ±3.77	14.91 ±3.03	11.41 ±2.19	11.42 ±2.44	71.03 ±14.93	5.93 ±1.20	5.32 ±0.82	0.15 ±0.02
	250 ppm	20	0.67 ±0.06	0.28 ±0.03	0.39 ±0.03	2.52 ±0.20	0.18 ±0.03	0.32 ±0.03	0.32 ±0.03	0.17 ±0.05	14.90 ±3.24	14.27 ±3.44	10.24 ±2.17	11.38 ±2.51	72.96 ±18.41	5.58 ±1.49	5.09 ±0.91	0.15 ±0.03
	1250 ppm	20	* 0.70 ±0.06	0.29 ±0.02	0.41 ±0.03	** 2.67 ±0.16	0.20 ±0.03	0.31 ±0.04	0.31 ±0.03	0.18 ±0.04	15.32 ±3.49	15.17 ±2.56	11.41 ±1.81	10.80 ±2.41	71.48 ±17.00	5.67 ±1.52	5.56 ±0.97	0.15 ±0.02
	9375 ppm	20	*** 0.78 ±0.07	*** 0.32 ±0.02	** 0.44 ±0.04	*** 3.72 ±0.26	0.21 ±0.04	*** 0.35 ±0.03	*** 0.35 ±0.04	** 0.23 ±0.06	14.65 ±2.89	15.08 ±3.52	*** 12.87 ±2.16	12.20 ±2.93	80.31 ±22.13	6.14 ±1.18	* 5.84 ±1.10	* 0.16 ±0.02

Mean±SD* P<0.05 ** P<0.01 *** P<0.001

Table 18 : Macroscopic findings in male and female rats

Sex			Male					Female				
Dose Level (ppm)			0	50	250	1250	9375	0	50	250	1250	9375
No of rats examined			20	20	20	20	20	20	20	20	20	20
Lung	:	Congestion	0	0	0	0	1	2	3	3	3	2
	:	Punctate hemorrhage	0	0	0	1	0	0	0	0	0	0
Liver	:	Nodule	0	0	1	0	1	0	0	0	0	0
Kidneys	:	Cyst	0	1	0	0	0	0	0	0	0	0
Pancreas	:	Focal steatosis	0	1	0	0	0	0	0	0	0	0
	:	Punctate hemorrhage	0	0	0	2	0	0	0	0	0	0
Pituitary	:	Hematoma	0	0	0	0	1	0	0	0	0	0
Thymus	:	Hemorrhage	0	1	0	0	0	0	1	0	0	0
Mesenteric lymph node	:	Enlargement	0	0	1	0	0	0	0	0	0	0
Ovaries	:	Abscess						2	2	1	3	4
	:	Hematoma						1	0	0	2	1
Uterus	:	Retention of clean liquid in uterus						1	3	2	0	10**

** Statistical significance ($p<0.01$) by Chi Square Test (with Yates correction)

Table 19 : Histopathological findings in male and female rats

Sex			Male					Female				
Dose Level (ppm)			0	50	250	1250	9375	0	50	250	1250	9375
Lung	:	Thickening of alveolar wall	11/20	3/20*	10/20	4/20	5/20	6/20	2/20	3/20	2/20	11/20
		Hemorrhage	0/20	0/20	1/20	0/20	0/20	0/20	0/20	2/20	0/20	0/20
Liver	:	Focal necrosis	0/20	0/20	1/20	0/20	1/20	0/20	0/20	0/20	0/20	0/20
Kidneys	:	Cyst	0/20	1/20	0/20	0/20	0/20	0/20	0/20	0/20	0/20	0/20
		Calcification	0/20	0/20	0/20	0/20	0/20	1/20	1/20	0/20	0/20	1/20
		Nephropathy in Pelvis	0/20	1/20	0/20	0/20	0/20	0/20	0/20	0/20	0/20	1/20
Pituitary	:	Congestion	0/18	0/20	0/20	0/20	1/20	0/20	0/20	0/20	0/20	0/19
Thymus	:	Hemorrhage	0/17	0/18	0/20	0/19	0/19	0/20	1/20	0/20	0/20	0/20
Mammary gland	:	Cyst						0/18	0/19	0/19	0/20	1/18
Ovaries	:	Congestion						1/20	0/20	0/20	1/20	0/20
		Follicular cyst						0/20	0/20	0/20	1/20	0/20
		Hypoplasia of Corpus luteum						0/20	1/20	1/20	1/20	1/20
Uterus	:	Dilatation						3/20	2/19	1/20	2/20	6/20

Denominator = No of animals examined

* Statistical significance ($p<0.05$) by Chi Square Test (with Yates correction)