



DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
PUBLIC HEALTH SERVICE
Washington, D. C.

103299

OF DISEASE PREVENTION
ENVIRONMENTAL CONTROL

November 9, 1967

REFER TO

Mr. Kenneth Nash
Pesticide Regulation Division
Agricultural Research Service
U. S. Department of Agriculture
Washington, D. C. 20250

Dear Mr. Nash:

The toxicological data on Dacthal received July 20, 1967 in connection with Reg Nos. 2393-176, 557-LE and 677-139 has been reviewed.

We concur with you in the registration of the chemical for the uses as stated on the labels.

If you have the data from the first and third breeding phases of the three generation rat reproduction study, we would appreciate receiving a copy.

Sincerely,

Robert D. Coberly
Biologist
Registration Section
Pesticides Program

003299

Summary

The data as reviewed shows the chemical to have a low degree of acute, subacute, and chronic toxicity. Lengthy exposure at elevated levels cause various levels of liver and spleen involvement. These are partly or totally reversible.

Dacthal

- ✓ Acute Rat Oral (Tech) : Male LD₅₀ = > 3160 mg/Kg
Animals receiving 100 mg/Kg or more
exhibited depression.
- ✓ Acute Rabbit Dermal (Tech) : LD₅₀ = > 10,000 mg/Kg
Moderate erythema and slight edema
(at the two high levels) were noted.
- ✓ Rabbit Eye Irritation : A mild degree of eye irritation for
24 hours was noted.
- Subacute Rat Feeding (Tech)
(28 day) : Levels tested were 0.0082, 0.0824
and 0.824% (or 82, 824, 8240 ppm).
No effects were noted at the levels
tested.
- Subacute 28 Day Dog Oral (Tech) : Centrolobular congestion of the liver
accompanied by degenerative changes
was noted.
- Subacute 30 Day Rat Feeding
(82.4% Pure) : Dosage level tested was 10,000 ppm.
Skin abrasions of the head were noted.
Body weight gain was inhibited. Liver
enlargement and spleen involvement
were noted. No effect level appears
to be = > 8240 ppm and < 10,000 ppm
(see 28 day rat feeding study).
- Rat Reproduction Study (Tech)
(Second Phase) : Data seems to indicate the animals
are in poor physical condition.
Reproductive indices are low.
- Rabbit Reproduction Study (Tech) : Dosage levels tested were 1,000 and
10,000 ppm. The test groups were
comparable to the control group.

Chronic Two Year Rat Feeding
(Tech)(Dacthal T)

: Levels tested were 100, 1,000, and 10,000 ppm. No dermal irritation was noted. In general the test animals were comparable to the controls as no consistent patterns were established.

Rat Reproduction Study
(Dacthal T)

: Levels tested were 1,000 and 10,000 ppm. No adverse effect on the breeding performance was noted.

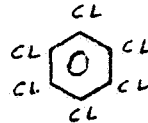
Two Year Dog Feeding
(Dacthal T)

: Levels tested were 100, 1,000, and 10,000 ppm. No adverse effects were noted.

Metabolism Study

: See report

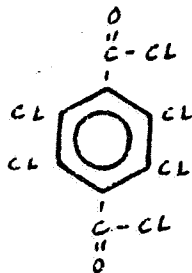
Hexachlorobenzene



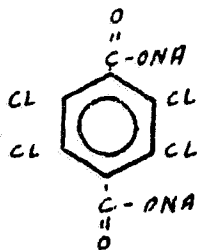
Subacute 90 Day Rat Feeding

: Levels tested were 5, 25, 125, and 625 ppm. The 5 and 25 ppm levels were comparable to the control group. Effects were noted at the 125 and 625 ppm levels.

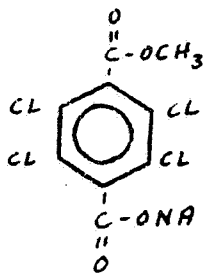
DAC-876 : Tetrachloroterephthaloyl Chloride (TTD)



DAC-1209 : Disodium 2,3,5,6-tetrachloroterephthalate



DAC-1563 : Methyl sodium 2,3,5,6-tetrachloroterephthalate



Subacute 28 Day Rat Feeding (DAC-876-1209-1563):

Level tested was 1.0% (10,000 ppm). No adverse effects were noted.

No deaths.

RDCoberly:deg
November 7, 1967

Dacthal

Acute Rat Oral (Technical)

Five male rats were tested per dosage level of 10, 31.6, 100, 316, 1000, and 3160 mg/Kg. Animals were fasted for a period of three to four hours prior to dosage. Gross autopsies were performed at the termination of the study.

Results

There were no mortalities at any dosage level tested. Thus the LD₅₀ = >3160 mg/Kg. During the day of administration the animals at the four higher dosage levels appeared depressed. Gross autopsies performed on all animals revealed no significant gross pathology.

Acute Rabbit Dermal (Technical)

Four rabbits were tested per dosage level of 316, 1000, 3160, and 10000 mg/Kg. The test material was moistened with sufficient 0.5% weight/volume aqueous methyl cellulose solution to form a paste. Exposure time was 24 hours.

Results

There were no mortalities at any dosage level. Thus the dermal LD₅₀ = >10000 mg/Kg. At 24 hours when the binders were removed, most or all of the applied material was found on the abdomens or binders. The exposed skin area showed a mild degree of dermal irritation which was characterized by mild or moderate erythema. In addition, one animal at each of the two

higher dosage levels exhibited slight edema. The edema subsided within 24 hours. The erythema gradually diminished in intensity but did not subside completely during the observation period of seven days. During the final few days of the observation period the exposed skin area generally showed slight erythema and slight atonia and/or desquamation. Autopsy revealed no significant gross pathological findings.

Acute Rabbit Eye Irritation

A single application of 3.0 mg of the test material was placed in the conjunctival sac of the left eye of three rabbits. The untreated eye served as a control. The treated eye was held closed for approximately 30 seconds following application, after which an immediate reading was made. Additional readings were made at 1, 4, 24 hours and daily thereafter for an additional six days.

Results

Immediately following eye application there was a mild degree of eye irritation which was characterized by erythema and vascularization of the sclera and nictitating membrane, accompanied by lacrimation. At 24 hours the treated eyes of each animal appeared grossly normal.

Subacute Rat Feeding (Technical) (28 day)

Forty male rats were tested per dosage level of 0.0082, 0.0824, and 0.824% (equivalent to 82, 824, and 8240 ppm). At 28 days all control and test rats were sacrificed and gross autopsies performed. The following

tissues from five rats of each group were preserved in 10% Formalin; lungs, heart, liver, spleen, stomach, small and large intestines, pancreas, kidney, adrenals, testis, bone and skin from the area between the eyes and the ears. Sections of the liver and skin were examined microscopically.

Results

No deaths occurred during this study. The gross appearance, behavior, body weight gains, food consumption, liver weights and liver to body weight ratios show no significant difference between the test animals and the control animals. The autopsies revealed no pathological findings which could be attributed to the dietary feeding of Dacthal. Microscopic examination of sections of the liver and skin revealed the tissues to be within normal limits.

Subacute 28 Day Dog Oral (Technical)

Two males and two females were tested at a dosage level of 800 mg/Kg/day. Test material was administered by capsule once daily, seven days a week, for four weeks. The liver, kidney and skin tissue were submitted for histopathological evaluation.

Results

Signs of apparent compound effect among the test dogs were; reduced appetite accompanied by a loss in body weight; decreased activity; and increased liver weights and liver to body weight ratios. The results of the hematological, biochemical, and urine studies were generally unremarkable.

No observable gross pathology was noted. Microscopic examination showed centrilobular congestion in the liver accompanied by degenerative changes.

Subacute 30 Day Rat Feeding (82.4% Pure)

Ten male rats were tested at a dosage level of 1% (10000 ppm).

Results

At the end of the second week several small skin abrasions were noted on the face and behind the ears of two test rats. During the third week seven test animals developed skin abrasions on the face, behind the ears and/or under the chin. Some of these abrasions gradually developed into deep sores. At the end of the fourth week, skin abrasions were noted in nine of the ten test animals. No signs of dermal irritation were noted on other parts of the body in any of the test animals. In addition to the skin condition, several test rats exhibited slight intermittent tremors during the fourth week.

Growth suppression in the test group was noted during the second experimental week and progressed until it was significantly lower at termination of the study. Food consumption of the test group was comparable to the control animals.

One death in the test group occurred. Gross autopsy revealed bright red colored lungs, a greatly enlarged liver (weight - 21.35 grams) black in color with pale areas on a dorsal surface of the lobes, a pale spleen, and slightly congested kidneys; the stomach and small intestines contained

a yellowish fluid and some gas; a very small amount of body fluid was found in the abdominal cavity. Slight signs of autolysis were noted in all organs and tissues of this animal.

Gross autopsies at termination revealed consistent and very marked enlargement of the liver in each of the test animals. The average liver weight for the test animals was 22.9 grams as compared to a normal liver weight range of 11 to 14 grams for rats of this age. No changes in the texture or color of the livers were observed. Other gross findings in the test rats were a pale or bluish-tinged surface at the spleen in three animals and dilation of the pelvis of the left kidney in one animal.

Comment

In combining the results of this study with the results of the 28 day rat feeding study it appears that the no effect level on a subacute basis for this chemical lies somewhere between 8240 ppm and 10000 ppm.

Rat Reproduction Study (Technical) (Second Phase)

Results of the F0 and the F1 generations are not included in this report. This report indicates the animals were tested at the dietary levels of 0.1 and 1.0%.

The P₂ parents were bred at approximately 190 days of age.

Results

Growth for the males in the two test groups were comparable with that for the control group. Body weight gains for the female test rats at both dosage levels were slightly below those for the female controls. Food consumption was comparable.

The fertility index for group number two (0.1%) was significantly higher than the indices for the control group and group number three (1%). The lactation for the litters in group number two was significantly lower than that for the controls; this difference was considered meaningless since only two control litters were available for comparison. The lactation index for group number three was lower than that for the controls but not significantly different. All remaining litter data were comparable among the test litters in the controls.

The pups of the two nursing litters in the control group had a normal appearance. Five of the twelve litters produced in group number two had normal healthy pups. In two litters the newborn pups appeared weak, bluish and cold to the touch and died within the first week. Sickly pups were also found in the remaining five litters and the mortality rate was high. The pups of two of the four nursing litters in group number three developed normally and all survived the nursing period. In the third litter all pups were small at weaning. The pups of the fourth litter appeared weak and

sick and only one of the eight pups survived. Autopsies performed on representative weanlings from the control and test litters did not reveal any gross change in the organs.

Comments

The report states that the poor reproductive performance of the second generation parents in all three groups, particularly in the control group, was attributable to the advanced age of the animals at the time of mating and also that there was no relation between the poor results and the feeding of the test material. These statements do not appear to be entirely accurate. If you were to consider the normal age of a parent at the time she is bred for the second generation (example - F1B) her age is in the range of 170 to 190 days.

I assume that these same parents are going to be bred for a third time, otherwise, I would have expected to encounter some histological examination of various organs. Another interesting factor which must be considered in this study and this is the fact that the high level, 10000 ppm produced liver enlargement and splenic involvement in the 30 day rat feeding study. This level should produce adverse effects on the animals so far as viability, general health and food consumption.

Rabbit Reproduction Study (Technical)

Six rabbits were tested per dosage level of 1000 and 10000 ppm. From the eighth through the sixteenth day of the gestation period, calculated from

the first mating, the dosage levels were fed to the appropriate test groups. On the seventeen day the animals were returned to the untreated diet. On the twenty-eighth or twenty-ninth day of the gestation period three pregnant females from each group were anesthetized and cesarean sections performed. The remaining does in each group were allowed to complete full term. The uteri of all animals were closely observed for sites of resorption and fetal attachment.

Results

Negative Control - Two animals in this group did not become pregnant.

Four normal size fetuses were recovered and four sites of resorption were noted at hysterotomy in the control animal which refused food on the first part of a gestation period. Another control animal, delivered by cesarean section, presented six normal size fetuses and three small fetuses which apparently failed to attain normal size, and one site of resorption. The other fetuses and young in all of the control litters show no gross abnormalities.

1,000 ppm Group - One of these animals had six normal size fetuses and one small fetus and another animal exhibited one site of resorption following hysterotomy. Definite sites of fetal attachment were noted in the uteri of two other

animals; however, several of these could not be accounted for. There were no gross abnormalities in any of the young or fetuses in this group.

10,000 ppm Group - One animal had two small sized fetuses along with six normal fetuses at cesarean section. These small fetuses were fully formed and presented no gross abnormalities. Three animals which delivered their young normally showed uterine sites of fetal attachment which exceeded the number of young born. These unaccounted for sites were believed to be those of young born dead and subsequently consumed by the mother. A partly eaten dead young was noted in each of the two litters. There were no apparent gross abnormalities in any of the young born normally or in the fetuses obtained by cesarean section.

Chronic Two Year Rat Feeding Study (Technical) (Dacthal T)

Thirty-five males and thirty-five females were tested per dosage level of 100, 1000, and 10000 ppm. Interim sacrifices were made at 13 and 52 weeks.

Results

The appearance and behavior of the test rats receiving Dacthal-T were generally comparable but those of the control animals throughout the two year period. No dermal irritation, skin lesions, or other signs of compound effect were noted among the test rats at any dietary level. Growth

for the males and females in all three test groups was comparable with that for the corresponding controls throughout the 104 week period. Food consumption from the twenty-eighth through the fifty-second week for the males in group three (1000 ppm) and for the males and females in group number four (10000 ppm) was significantly higher as compared with the corresponding controls. Food consumption for the control and test groups during the second year was not elevated statistically; however, inspection of the data revealed higher weekly mean values from the eightieth through the one hundred and fourth week for the males in group four and the females in group three and four as compared to the control values. No gross pathology was noted at any sacrifice period which could be attributed to the ingestion of the test material.

Organ Weights - At 13 weeks the females in the 10000 ppm level revealed a significantly higher liver ratio. The females of the 100 ppm level showed a significantly higher adrenal ratio. The adrenal ratio for the males in the 1000 ppm was found to be significantly lower those of the control males. There appears to be little meaning for relationship in the variations in the adrenal ratio to dose. At 52 weeks, statistical analysis revealed that all values of the test animals were comparable to the control values. At 104 weeks, the kidney weight for the males in group number four and the adrenal ratio for the females in group number three (1000 ppm) were found to be significantly higher than those for

the corresponding controls. A fairly large variety of tumors was encountered. But there appeared to be no apparent relationship between the tumors and the ingestion of the test material.

Microscopic examination of organs from a large number of control and test male and female rats after 104 weeks of administration revealed no histologic difference attributable to the ingestion of the test material.

Rat Reproduction Study (Dacthal T)

Ten males and eighteen females were tested per dosage level of 1000 and 10000 ppm. The breeding phase was conducted using sixteen females and eight males for each group. The criteria chosen for statistical evaluation of the litter data for the indices of fertility, gestation, live birth and lactation.

Results

F_{1A} - The lactation index for the litters in the 10000 ppm were significantly lower than the controls. The fertility indices for both test groups, the lactation index for the 1000 ppm and the weight of the pups in the 10000 ppm level at weaning were lower than, but not significantly different from those for the control litters. All remaining data were comparable. Small, thin or sickly appearing pups were more frequently found among the nursing litters in the 10000 ppm level.

F_{1B} - The lactation index for the litters in the 1000 ppm level was significantly lower than those for the control litters; however, the lactation index for the 10000 ppm level was slightly higher than that for the control. There were no significant differences between the other indices for the test groups and those for the control groups. Comparison between the data for the F_{1A} and F_{1B} litters revealed no meaningful difference.

Two Year Dog Feeding (Dacthal T)

Four male and four female pure bred beagles were tested per dosage level of 100, 1000, and 10000 ppm. At the end of the first year one male and one female from the control and each of the test groups was sacrificed. At the end of two years all of the animals except one female from each group was sacrificed and the organs weighed. These female dogs were sacrificed during the one hundred and fourteenth week of the study.

Results

The general appearance and behavior of the test animals were comparable to those of the control animals.

In general, the hematological picture for all four groups of animals appear to be comparable and there is no evidence of any toxicological effect.

The organs of the male and female dogs receiving Dacthal T at the three different dosage levels presented histologic variations which were not consistent and not indicative of a compound effect.

Metabolism Study

Through the use of fresh beef liver in contact with pure Dacthal, it was determined that the enzymes present in the liver could hydrolyze Dacthal to the monomethyl ester of tetrachloroterephthalic acid (DAC-1449). Examination of the excreta from the dogs in the two year dietary feeding study showed that the bulk of the Dacthal was eliminated unchanged in the feces. A substantial portion of Dacthal had been converted to DAC-1449 and eliminated through the urine. A much smaller amount of a second metabolite, identified as tetrachloroterephthalic acid (DAC-954) was found in the urine. Based on these results a in-vivo metabolism study was conducted using two levels of each pure Dacthal and DAC-954, each level replicated three times. The compounds were administered in a single dose orally by capsule. Urine, feces, and blood were collected and analyzed for Dacthal, DAC-1449 and DAC-954 over a 96 hour period. Average total recoveries of the Dacthal were 86% for the higher dosage and 71% for the lower dosage. At both levels 97% of the total Dacthal found was eliminated unchanged in the feces. Approximately 3% of the Dacthal was converted to DAC-1449; 2% of which was eliminated in the urine; 1% was found in the feces. There was an average of 0.07% of the Dacthal converted to DAC-954, which appears in the urine. No Dacthal could be detected in the blood; however, both DAC-1449 and DAC-954 were detected. Both metabolites disappeared from the blood before termination of the test.

Data obtained on the metabolism study with the DAC-954 shows that 80 to 90% of the material was eliminated in the feces; the remainder was eliminated unchanged in urine. The concentration of DAC-954 in the blood reached a maximum at both levels within the first three hours; decreased rapidly so that by the end of the twelfth test hour none could be detected. All the DAC-954 administered was recovered during the test period. No further breakdown product was noted.

Upon termination of the test, the liver, kidney and fat of each test animal was analyzed for both Dacthal and its metabolites. There was no residual chemical in the organs from the DAC-954 test. The organs from the dogs in the Dacthal test did not contain any of the two metabolites and only trace quantities of Dacthal.

Comment

The protocol of these studies is listed in the text of these reports submitted by the company.

Subacute Twenty-Eight Day Rat Feeding (DAC-876-1209-1563)

Ten male rats were tested at a dosage level of 1.0% for each of the individual chemicals (3). Following a 28 day feeding period all control and test rats were sacrificed and complete autopsies performed on five animals from each group. Liver and kidney weights from five animals from each level were recorded. Liver to body weight and kidney to body weight ratios were determined. The following tissues from five rats

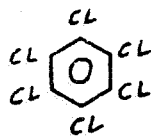
from each group were preserved in 10% Formalin: heart, lung, liver, spleen, stomach, small intestine, large intestine, pancreas, kidney, adrenal, testis, bone and skin from the area between the eyes and the ears.

Results

The general physical appearance and behavior of the test rats of each group was comparable to that of the control rats. Body weight gains, terminal body weights, and total food consumption was also comparable to the controls. The statistical analysis of liver weights, liver to body weight ratio, kidney weights, and kidney to body weight ratios show no significant difference the control and any test group. Autopsies performed on five control and five test animals sacrificed after 28 days of feeding revealed no pathological findings which could be attributed to the dietary feeding of DAC-1563, DAC-1209, or DAC-876.

RDCoberly:deg
November 7, 1967Hexachlorobenzene

Caswell #477

Subacute 90 Day Rat Feeding

Ten males and ten females were tested per dosage level of 5, 25, 125, and 625 ppm. All test rats were observed daily for signs of toxic or pharmacologic effect, and particularly for signs of dermal irritation and/or lesions around the head and forepaws. After 21, 45, and 90 days hematological studies were performed on five animals of each sex of each group including the controls. At 13 weeks the following tissues from each animal sacrificed or preserved brain, pituitary, thyroid, lungs, heart, liver, spleen, kidneys, adrenals, stomach, pancreas, small and large intestines, urinary bladder, gonads, bone, bone marrow, and skin. These tissues from each control rat and each rat in the 625 ppm level were examined microscopically. The remaining five rats of each sex in the 125 and the five males and four females in group number five (625 ppm) were maintained on the basal laboratory diet for a two week recovery period and were then sacrificed and autopsies performed.

Results

The physical appearance and behavior of the rats in the three lower dosage levels were generally comparable to those of the controls. No dermal irritation, skin lesions, or other signs of toxic or pharmacologic effect were noted among the rats in these groups.

The rats in the 625 ppm level showed signs of marked respiratory involvement, a hunched position of the body, and abdominal fur stained with urine. After the fifth week many animals in this group were noted to have slight tremors. This condition was not persistent, but was observed intermittently in different animals and became more pronounced toward the end of the 13 week period. Small sores on the head or neck and/or alopecia were noted in six females of this group. Among the nine animals in this group which were maintained on control feed for a two week recovery period, seven showed an improvement in appearance. The males in the 625 ppm level showed a weight inhibition and also a reduction in food efficiency. Survival was comparable among the control and test groups. One female in the 625 ppm level died in the eighth week of the study. There were no other deaths.

The total leukocyte counts at 21 and 90 days for the males and at 21, 45, and 90 days for the females in the 625 ppm level and percentage of segmented neutrophils in the differential at 21 and 45 days for the males and females in the 125 ppm and 625 ppm levels were noticeably higher than the corresponding controls. The cell volume values at 21 and 90 days for the females of the 625 ppm level were lower than those for the corresponding female controls.

The male animals of the 625 ppm level showed a significant increase in the absolute weight of the thyroid, liver, and adrenals. These same animals showed a significant increase in the organ to body weight ratio of the thyroid, liver, spleen, kidneys, adrenals and testes. The females of this dosage level showed an increase in the absolute weight of the liver and spleen. They also showed an increase in the organ to body weight ratio of the liver, spleen and kidneys.

Gross Pathology - The first three levels did not reveal any consistent gross changes. The 625 ppm animals had markedly enlarged and thickened livers with rounded margins and pitted surface; the cut surface revealed a granular texture of the lobes. Slight to marked enlargement of the thyroid was evident in all ten animals and the kidneys of two males appeared pale. No gross changes in the other organs were noted.

Microscopic examination of the test animals showed consistent alterations in the liver of the animals in the 125 and the 625 ppm levels. These changes increased in severity with an increased intake of the test material. Changes of a less distinct and less consistent nature were observed in the thyroid, kidneys, adrenals, and bone marrow of the test animals.

The livers of all ten rats at the 625 ppm level which were examined showed the following degenerative changes; distortion of the lobe caused by greatly enlarged parenchymal cells in the central area, peripheral

compression of the normal basophilic cytoplasmic granules against the cell wall, focal loss of cell outline in the central areas, only occasional single vacuoles, the formation of entracytoplasmic eosinophilic masses, and nuclear variations in size and staining. These were more marked in the males but also present to a lesser degree in the females. In the more advanced lesions these changes were accompanied by various degrees of mitotic activity and focal cellular necrosis. Outside of the area of alteration, the hepatic cells were of normal size and structure.

Most of the liver sections from the 125 ppm level showed the same cellular changes as those described for the 625 ppm although to a lesser degree and less in the females than in the males.

The thyroid sections from the animals in the 625 ppm all showed some degree of hyperplasia, although in two instances it was considered minimal in the females. In the areas of hyperplastic changes the follicles were lined by somewhat irregularly enlarged, plump, cuboidal to low columnar epithelium and frequently had secondary lumina.

The kidney sections for most of the animals of the 125 and 625 ppm revealed a slight degree of granular degeneration in the proximal tubules. Foci of regenerative tubular epithelium in the deeper cortical area were discovered in kidney sections from four males in the high level and from one male and one female in the 125 ppm group, but not in the control animals.

Adrenal sections examined from animals in the 125 and 625 ppm groups revealed in many instances slight alterations in the cortical structure in which the zona fasciculata was slightly increased in width and the cells were enlarged and showed increased cytoplasmic vacuolization and granularity, particularly in the outer part of the zone. Enlargement of the cells sometimes extended to the inner zone, which in one instance, was particularly nonexistent. These changes are considered indicative of increased stimulation of the gland. The zona glomerulosa appeared somewhat broad and the cells usually had a good to high lipid content. In one instance, the adrenal of a male in the 125 ppm group showed irregular loss of lipid characterized by eosinophilic changes in the cortical cells. The adrenals of the rats in the 25 ppm group did not reveal any significant alterations.

Microscopic Examination - Sections of the pituitary, heart, lung, spleen, pancreas, and gonads from the high level test rats did not disclose any alterations which could be associated with the ingestion of the test material.

Autopsies performed on the test animals at the end of the two week recovery period revealed slightly enlarged livers in two males and congested livers in two females in the 125 ppm group. All males and females in the 625 ppm group had markedly enlarged livers with thickened lobes, a pitted surface and a granular cut surface. Additional coincidental findings in the 625 ppm group included congested thyroids in two males, pale appearing kidneys

in one male, and slightly enlarged spleens in two females. The male rats at the 625 ppm level showed a significant drop in liver to body weight ratio during the recovery period and the females at the same level showed a rise in the kidney to body weight ratio. Microscopic examination of test organs from the animals in the test groups revealed degenerative changes in the livers of the animals in both groups. The livers of the five males and four females in the 625 ppm group presented alterations similar to those described for other animals in this group which were sacrificed while receiving the test material. These changes were more advanced in the males than in the females and were characterized chiefly by enlargement of the centrilobular cells, peripheralization of the normal basophilic granularity, occasional vacuolization and focal cellular necrosis with increased mitotic activity in the more advanced lesions.

The thyroid sections of several animals in the 125 ppm group and the majority in the 625 ppm group showed signs of slight to moderate increase in activity characterized by irregular enlargement and vascularization of the epithelium, depletion of colloid within the lumen, formation of secondary lumina, and the presence of interfollicular epithelial nests.