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July 13, 1995

Document Processing Center (TS-790)
ATTN: Section 8(e) Coordinator
Office of Toxic Substances
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460



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Dear Sir:

Bayer Corporation is submitting a copy of a report we just received as requested from the FDA files on e-Caprolactam, CAS# 105-60-2 as reported by Dr. Robert MacFate dated January 24, 1962.

This report contains the results of toxicity studies that were performed on e-caprolactam in rats (subacute through chronic, plus reproduction and metabolism) and dogs (chronic toxicity and metabolism only). Findings that were common to both the rats and dogs involved the induction of anemia/hematopoietic changes that were recorded in the later stages of the chronic rat and dog studies, starting at 500 mg/kg/dy for the rats and at 250 mg/kg/dy for the dogs. Also observed for both test species at these high dose levels were organ weight changes involving liver, spleen, kidney and lung indicating possible involvement of these organs in the metabolism of this compound and/or as target organs. These gross observations were supported in necropsy (edema and congestion, particularly in the liver and kidneys) as well as in histopathology (focal degeneration/necrosis of hepatic parenchymal cells, degeneration of glomeruli and renal tubules, and hemosiderosis).

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To our knowledge, this set of results have not been previously submitted to the EPA, nor can we find where they have been published in the scientific literature. Even though this report is old, (i.e 1962) and the studies deficient by today's standards, these results warranted reporting under TSCA, Section 8(e) according to EPA Reporting Guidance Document. We have also reported this information the EPA under Section 8(d).

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EPA 8(e)

Please contact me if you have any questions.

Sincerely,



Donald W. Lamb, Ph.D
Vice President
Product Safety & Regulatory Affairs
412-777-7431

95-2-15.doc:vmk
Attachment
Certified Mail: P 921 654 924

January 24, 1962

Subject: Studies on E-Caprolactam. Subacute Toxicity, Chronic Toxicity, Reproduction and Metabolic Studies.

Test Material: E-Caprolactam wash water received from Mr. A. J. Sweet, Manager of Development, Chesterfield Plant, National Aniline Division, Allied Chemical Corporation, Hopewell, Virginia. Each shipment was identified by a code number and the lactam content of the solution given. This concentration was checked. Dosages were determined on the basis of the caprolactam in the solution.

Test Procedures: The test procedures and the detailed findings follow.

Conclusions: Subacute toxicity studies in rats showed that the test material had a relatively low toxicity and that the animals possessed an efficient system for detoxifying the E-caprolactam. Rats fed 57% of the LD₅₀ of caprolactam (amounting to 1,000 mg./kg./day) for a period of 90 days showed no clinical symptoms and only very minor changes in the liver tissue.

Chronic toxicity studies in rats again confirmed the low toxicity of the test material and the efficiency of the detoxifying mechanism. Rats fed 100 mg./kg./day of the test material for a period of two years showed no differences from the control rats in so far as general health, longevity, body weights, organ weights, blood findings, and tissue findings were concerned. It is to be noted that 100 mg. of the test material per kg. of body weight is at least 1,000 times the amount of the test material that a person could be expected to consume in a day.

While the rats receiving 500 mg./kg./day and those receiving 1,000 mg./kg./day did show toxic changes, it is to be noted that 7 out of 10 male rats and 8 out of 10 female rats were still alive after 24 months of daily feeding of 57% of the LD₅₀ of the test material (amounting to 1,000 mg./kg./day). It is to be noted that 24 months is close to the normal life span of rats of this type and breed.

Reproduction studies in rats showed that the ingestion of 100 mg./kg./day of the test material had no effect on reproduction through three successive generations of rats.

Chronic toxicity studies in dogs again confirmed the low toxicity of the test material and the presence of an efficient detoxifying mechanism. Dogs fed 100 mg./kg./day of the test material for a period of two years and four months showed no differences from the control dogs in so far as general health, longevity, body weights, organ weights, hematologic findings, blood chemistry findings and tissue findings were concerned.

Metabolic studies lead to the conclusion again that the animals tested possessed an efficient detoxifying mechanism for the test material. Apparently the liver is the site of detoxification. Urea and glycine, and possibly other related compounds, take part in the detoxification.

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With the ingestion of small amounts of E-Caprolactam, the liver converts it to E-amino caproic acid and other metabolites which are excreted in the urine, as shown by paper chromatography. With the ingestion of larger amounts of E-caprolactam, some free E-caprolactam may be excreted unchanged in the urine. When the ingestion of E-caprolactam is stopped, the urines and tissues revert to their normal composition in one or two days, indicating that there is no cumulative effect.

It is concluded from these facts and the detailed studies following that the test material, E-caprolactam and any polymers present in the wash water, in the amount of 100 mg. per kg. of body weight can be consumed daily with no damaging effect to the animal organism.

R. P. MacFate

Subacute Toxicity Studies in Rats.

Test Animals. Sprague-Dawley white rats, weanlings. One week on normal diet after receipt. Then the test procedure was instituted. Ten males and 10 females were used for each dosage level.

Dosage Levels. The following amounts of the test material were administered: 0, 5, 50, 100, 250, 500 and 1,000 mg. per kg. per day. (These were chosen on the basis of the oral LD50 of 1,750 mg. per kg. of body weight.)

Test Procedure. Amounts of the test material were added to the prepared diet according to the dosage to be administered, the weights of the rats, and the amount of food being consumed. Food lost was weighed and replaced. The amount of the test material was adjusted daily and then weekly. Water ad lib. The rats were observed clinically each day, weighed as required, bled for hematologic study, sacrificed and the tissues studied grossly and microscopically after autopsy.

Half of the rats, 5 males and 5 females at each dosage level, (a total of 70 rats including 10 control), were fed for 60 days and then sacrificed. The balance of the rats, 5 males and 5 females at each dosage level, (a total of 70 rats including 10 controls), were fed for 90 days and then sacrificed.

Findings.

1. Rats Fed for 60 Days. At all dosage levels: No clinical symptoms, no mortality, normal food consumption, normal growth, normal blood findings, normal bone marrow, no gross pathology, no microscopic pathology.

2. Rats Fed for 90 Days. At all dosage levels: No clinical symptoms, no mortality, normal food consumption, normal growth, normal blood findings, normal bone marrow. There was no gross pathology except for a very slight mottling of the surface of the liver in 3 out of 10 rats at the 1,000 mg. dosage level. There was no microscopic pathology except a very small amount of nuclear aberration of a mild type in the liver and some slight cytoplasmic changes which could be consistent with a very mild toxic reaction, but the degree was minimal, in 6 out of 10 rats at the 1,000 mg. dosage level.

3. Conclusion. The above findings show that the test material has a low toxicity and that the rats probably have an efficient system for detoxifying the test material. The indication is that the test material must be fed in rather large amounts in an attempt to show what toxic changes will be produced, if any, by long term feeding.

Chronic Toxicity Studies in Rats.

Test Animals. Sprague-Dawley white rats, weanlings. One week on normal diet after receipt. Then the test procedure was instituted. Ten males and 10 females were used for each dosage level.

Dosage Levels. Food wrap, made of caprolactam polymer film, on one pound of various foods would contain about 2.5 mg. of extractables. If a 25 kg. child ate one pound of this food each day, and if all of the extractables were absorbed by the foods, the ingestion would amount to about 0.1 mg. per kg. per day. For adults, the weight ingested per kg. of body weight would be less than for a child. It is unusual for foods so-wrapped to be eaten daily to the extent of 1 pound.

The first dosage level for a chronic toxicity experiment is often taken at 100 times the possible daily rate of ingestion. Using the above figure of 0.1 mg., one hundred times would amount to 10 mg. per kg. of body weight per day. In the light of an LD₅₀ of 1750 mg. and the relatively negative findings in the subacute study, this is a very small dosage. Accordingly, a low level of 100 mg. per kg. of body weight per day was chosen. This is 1,000 times the probable daily rate of consumption. Rats were also fed at 500 and 1,000 mg./kg./day.

Test Procedure. Amounts of the test material were added to the prepared diet according to the dosage to be administered, the weights of the rats, and the amount of food being consumed. Food lost from the feeder was weighed and replaced. The amount of the test material was adjusted daily and then weekly. Water ad lib.

The rats were observed clinically each day, weighed daily, and as they grew older, weekly. Blood studies were made and, upon death or sacrifice, the organs were weighed. Gross and microscopic studies were made of the tissues, and the bone-marrow examined.

The rats were fed for approximately 730 days. With the weaning period, this gave a total of approximately 760 days of life. At the end of the feeding period, all rats still alive were sacrificed and autopsied.

Findings.

1. General Health. The general health of the rats during the study was excellent. No bacterial infections developed except for a few cases of pneumonia and most of these occurred in the latter part of the rats' lives. No parasitic infestations developed, either externally or internally. No ear infections developed. No worms. The 1,000 mg. test animals, males, became somewhat "shaggy" in appearance during the final months of life. The females, in contrast, were normal in appearance.

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2. Longevity. The number of rats receiving caprolactam and surviving to the end of the experiment were only slightly fewer in number than the controls that survived: 7, 8 and 7 males at the three feeding levels as compared to 8 controls; and 9, 9 and 8 females as compared to 10 controls. (See Table 18.) Further, the immediate causes of death in all the rats that died were infections not associated with the test material.

That the test animals possessed an efficient detoxifying mechanism is shown by the fact that 7 males out of 10 and 8 females out of 10 lived for a period of 25 months, during the last 24 months of which a daily ingestion occurred of 57% of the LD₅₀ (1,000 mg. per kg. per day) of the test material.

3. Body Weights. The body weights of the 4 groups of rats, (controls, 100 mg., 500 mg., and 1,000 mg. per kg. per day), at approximately 100 day intervals are shown in Tables 1, 4, 7 and 10. The relationship of these weights is seen in Figure 1.

The control males, at their maximum weight level, weighed from 150 to 180 grams more than the females. This is normal. In the controls, this maximum weight level was attained at sacrifice or about one or two weeks previous to sacrifice. (See Tables 3, 6, 9 and 12.)

The 100 mg. rats showed no material difference in average weight from the controls of the same sex, except that their maximum weight was attained on the average about 1 month before sacrifice. (See Fig. 1.)

The 500 mg. rats attained an average maximum weight of some 60 to 90 grams less than the controls and 100 mg. group. The maximum weight was attained, on the average, about one year before sacrifice in the case of the males, although in the females this occurred on the average only 3 months before sacrifice. Four females reached their maximum weight within the last month before sacrifice, similar to the controls. The final average weights of the males and females were from 70 to 130 grams less than the controls and 100 mg. group. (See Fig. 1.)

The 1,000 mg. rats attained an average maximum weight of some 100 to 160 grams less than the controls and 100 mg. group. The maximum weight was attained, on the average, over one year before sacrifice in the case of the males, although in the females this occurred on the average only about 3 months before sacrifice, as in the case of the 500 mg. group. Four females reached their maximum weight within the last month before sacrifice, similar to 4 of the females in the 500 mg. group. The final weight averages of the males and females were from 120 to 290 grams less than the controls and 100 mg. group. (See Fig. 1.)

It is concluded from the longevity and body weight patterns of the rats that the 100 mg. of test material per kg. of body weight per day had no visible clinical effects on the rats.

4. Organ Weights. The organ weights at sacrifice are given in Tables 2, 5, 8 and 11. These organ weights were calculated to grams per 100 grams of body weight, as shown in Tables 13, 14, 15 and 16, and are summarized in Table 17.

The organs of the 100 mg. group show essentially little difference in weight from the controls.

The organs of the 500 mg. group show a possibly significant increase in the weights of the heart and kidneys in both sexes, and possibly a significant increase in the female lungs and liver.

The organs of the 1,000 mg. group show a definite increase in the weights of the heart, lungs, liver, kidneys, and possibly the spleen. These indicate definite involvement of the cardio-vascular-renal system, with some edema and congestion.

5. Hematology. The controls and the 100 mg. group showed normal findings throughout life. See Tables 19 and 19A.

The 500 mg. group at 24 months showed a slight anemia on the basis of the decreased hemoglobin content of the blood and the morphology of the erythrocytes. There was a slight increase in the neutrophilic leukocytes, both relative and absolute.

The 1,000 mg. group at 18 months showed a slight anemia which developed at 24 months into a marked anemia. The anemia was more marked in the males. There was an increase in the neutrophilic leukocytes, both relative and absolute. The bone marrow at sacrifice showed an increased myeloid proliferation with some normoblastic hyperplasia.

6. Pathology. Tables 3, 6, 9 and 12 show a summary of the clinical, gross and microscopic pathology of the individual rats. Table 18 shows a summary by groups.

Table 18 shows the number of deaths due to infections. Seven male rats (out of 40) died of pneumonia, 1 of peritonitis, 1 of general septicemia, and 1 from an unknown cause; a total of 10 out of 40 rats, (2 from the controls). Four female rats (out of 40) died of pneumonia. Pneumonia is a common cause of death in rats.

Some of the female rats of the controls, and of the 3 groups fed the test material, developed fibroadenomas. These were benign tumors common in all breeds and strains of rats and were not produced by the test material. Four female controls out of 10 developed these tumors and the incidence was no greater in the female rats fed the test material.

Table 18 also summarizes the pathologic findings. The control rats and the 100 mg. group showed no pathology related directly to the ingestion of the test material. Any changes seen were due to old age, dietary factors other than the test material, infections and other conditions known to be unrelated to the ingestion of a toxic material.

In the 500 mg. group, 5 out of 10 males and 4 out of 10 females showed pathology, presumably related to the test material. Areas of nuclear changes and focal necrosis were seen in the livers. Anemia developed and hemosiderin was seen in the histiocytes of the spleen, due to the destruction of erythrocytes and hemoglobin. Kidney changes were seen, primarily in the glomeruli. These changes, while minimal in some cases, were consistent with an intoxication of chemical origin.

In the 1,000 mg. group, all 10 males and all 10 females showed pathology, presumably related to the test material. Some of the rats were emaciated and anemic. All weighed markedly less than the controls. Toxic changes in the liver, kidneys and spleen were more pronounced than in the 500 mg. group. The males appeared to be more severely affected than the females.

Conclusion. It is concluded that feeding rats 100 mg. of the test material per kg. of body weight per day had no effect on the general health, longevity, body weight, organ weights, blood findings and tissue findings of the rats.

Because of a possible sex difference in the toxicity of the test material, reproduction studies were pursued.

Test Animals. Sprague-Dawley white rats, weanlings. One week on normal diet after receipt. Then the test procedure was instituted. Twenty females and 20 males were used as controls and a like number were given the test material in their diet.

Dosage Level. The rats were given the test material in the amount of 0 and 100 mg. per kg. of body weight per day.

Test Procedure. The sexes were kept separated and fed for 90 days. Twenty females and 20 males from the controls and a like number on the test diet were then paired for breeding. The males were separated when obvious pregnancy had been achieved. The diets were continued.

After delivery and weaning of the "First Generation", the females were again bred and this was later repeated; 3 pregnancies in all. The first litter was carried further in these studies. The 2nd and 3rd litters were carried to the weaning stage and then sacrificed.

The pups from the first pregnancy (First Generation) were weaned. Twenty females and 20 males from different litters were chosen, and the sexes kept separated. Those from the controls were fed the normal diet and those from the mothers receiving the test material received this same diet.

After 90 days, the rats were paired for breeding the "Second Generation." The males were separated when obvious pregnancy had been achieved. The diets were continued.

After delivery and weaning the Second Generation, these females from the First Generation were again bred twice more; 3 pregnancies in all. As before, only the first litter was used for further studies. The 2nd and 3rd litters were carried to the weaning stage only.

The pups from the first pregnancy of the Second Generation were weaned. Feeding and breeding was repeated as before to obtain the "Third Generation".

Findings. The findings are summarized in Table 20. From the original pairs of control and test rats, the numbers of pups born (the First Generation) in 3 consecutive pregnancies, the number surviving more than 1 day, and the number of these weaned were counted. This record was maintained to the delivery and weaning of the Third Generation.

The fertility of the rats is shown by the number of pups born and the average number of pups per litter. The pups surviving more than one day, best expressed in terms of the per cent of the pups delivered, is an index of the viability of the pups. The pups weaned, best expressed as the per cent of the pups surviving more than one day and reaching the weaning period, is an index of the lactation ability of the rats.

In both the controls and the test-fed animals, the number of pups born and the average pups per litter were within normal limits. In addition, the number of pups surviving more than one day and the number of pups surviving to the weaning period were comparable.

Conclusion. It is concluded that feeding rats 100 mg. of the test material per kg. of body weight per day, had no effect on the reproduction of these rats through three generations.

Test Animals. Mixed breed dogs, primarily of the terrier breed. Ten dogs were used. The age at the beginning of the study varied from 6 months to 1 year.

Dosage Levels. The following amounts of the test material were fed to the dogs:

2 dogs(male & female)	-	0 (controls)	
2 dogs(male & female)	-	100 mg./kg./day	
1 dog (male)	-	250	"
2 dogs(male & female)	-	500	"
1 dog (female)	-	750	"
2 dogs(male & female)	-	1,000	"

Test Procedure. Amounts of the test material were added to the prepared diet according to the dosage to be administered and the weights of the dogs. Food lost from the feeder was replaced. The amount of test material was adjusted weekly. Water ad lib.

The dogs were observed clinically daily, weighed weekly and then biweekly. Blood studies were made. Upon death or sacrifice, the organs were weighed, gross and microscopic studies performed on the tissues, and the bone marrow examined.

The dogs were fed approximately 854 days (122 weeks). At the end of this period, all surviving dogs were sacrificed.

Findings.

1. General Health. The general health of the dogs was excellent. One dog died of pneumonia at about 21 months and another developed pneumonia and a general septicemia and was euthanized at 22 months. There were no parasitic infestations and no ear or other skin infections. No worms. The dogs receiving 1,000 mg./kg./day of the test material ate less than the other dogs of equivalent size, probably due to the bitter taste of the test material. The amount of food containing the test material was reduced and after this was eaten, further food without the test material was given.

2. Longevity. As noted above, 2 of the dogs died of pneumonia at 21 and 22 months. The other 8 dogs lived for the entire period of 122 weeks. Again the fact that 2 of the dogs survived for 122 weeks with a daily ingestion of 57% of the LD₅₀ (1,000 mg./kg./day) of the test material, attests to the presence in the dogs of an efficient detoxifying mechanism.

3. Body Weights. The body weights of the dogs are shown in Table 21. With mixed breed dogs and no certainty as to the exact date of birth, little can be drawn from the actual weights per se. For this reason, the per cent change in body weight was calculated and is shown on Table 22.

On Table 22 it will be noted that the control animals gained weight more or less steadily. The male gained 41% over the starting weight. The female had gained 36% over the starting weight at 72 weeks, subsequent to which pneumonia and septicemia developed. The dog became so ill clinically that death was a matter of hours and the animal was euthanized.

The dogs on 100 mg./kg./day gained weight more slowly than the controls, again possibly due to the taste of the food. One of these dogs developed pneumonia and died at 22 months.

The dog on 250 mg. gained weight to the same extent as did the control that lived to the end of the study.

The dogs on 500 mg. gained weight more slowly, one ending at a level below the starting weight.

The dogs receiving 750 mg. and 1,000 mg. gained very little weight during the test period and ended with a weight below the starting level.

4. Organ Weights. The organ weights at sacrifice are given in Table 23, and the weights per 100 grams of body weight in Table 24.

The weights of the various organs are within normal limits for the first seven dogs with few exceptions. This covers the controls and the dogs receiving 100, 250 and 500 mg. of test material per kg. per day. One dog receiving 500 mg. had a heart that appeared to be slightly heavier than the others.

The dogs receiving 750 and 1,000 mg. per kg. per day of the test material, showed some increase in the weight of the heart and a definite increase in the weights of the liver, kidney, spleen and lungs. This would be expected with the edema and congestion noted on autopsy and with the liver and renal lesions noted on histologic examination.

5. Hematology. The controls and the 100 mg., 250 mg., and 500 mg. dogs showed normal blood findings throughout life. See Tables 25 and 25A.

Dog 2 that died of pneumonia and septicemia showed in the bone marrow at death a very slight granulocytic hyperplasia and some immaturity but this was minimal.

Dog 7 on 500 mg. showed a very slight erythroblastic hyperplasia and this also was minimal.

Otherwise, the bone marrow in the above dogs was normal.

Dog 8 on 750 mg. and dogs 9 and 10 on 1,000 mg. showed a low hemoglobin concentration and a slight erythroblastic hyperplasia in the bone marrow. Otherwise the blood findings were within normal limits.

6. Blood Chemistry. The study was limited to glucose, urea nitrogen and serum protein. It was felt that this would give a sufficient picture of the general nutritional state of the animals and some idea of pathology, if it occurred, in the liver and kidneys.

The controls and the dogs on 100, 250 and 500 mg. showed normal findings with no significant changes throughout life. See Tables 26 and 26A. There appeared to be a slight decrease in the serum protein concentration at 24 months in one of the dogs (No. 7) on 500 mg. of test material.

Dog 8 on 750 mg. showed at 24 months a slight increase in the urea concentration and a possibly significant slight decrease in the serum protein.

Dogs 9 and 10 on 1,000 mg. showed at 24 months a definite increase in the urea concentration and a definite decrease in the serum protein. These indicated definite involvement of the liver and the low state of nutrition of the animals, since, as noted above, they were all losing weight.

7. Pathology. Table 27 summarizes the pathologic findings.

As previously noted, Dog No. 2 (female control) developed pneumonia and a generalized septicemia. Gross and microscopic findings confirmed this diagnosis. There was no other pathology in the various organs, with the exception of an early endocarditis.

Dog No. 4 (female on 100 mg.) also died of a pneumonia with the characteristic findings.

Dogs No. 1 (male control), No. 3 (male on 100 mg.) and No. 5 (male on 250 mg.) showed no pathology.

Dog No. 6 (male on 500 mg.) showed no pathology other than a slight inflammation in the parenchymal cells of the liver.

Dog No. 7 (female on 500 mg.) showed a few focal areas of degeneration in the liver, infiltrated with phagocytic cells, and some inflammation in the parenchymal cells, although all this was minimal.

Dog No. 8 (female on 750 mg.) showed small foci of degeneration in the liver with deposits of blood pigment throughout the liver. The kidney showed cloudy swelling.

Dog No. 9 (♂ male on 1,000 mg.) showed some degeneration of cord and parenchymal cells in the liver with deposits of blood pigment. The kidney showed some degeneration of the glomeruli and tubules. The spleen showed hemochromatosis.

Dog No. 10 (female on 1,000 mg.) showed the same findings as Dog No. 9 with the addition of cloudy swelling in the areas surrounding the islet cells of the pancreas.

Conclusions. It is concluded that feeding dogs 100 mg. of the test material per kg. of body weight per day for a period of 2 years and 4 months, had no effect on the general health, longevity, body weights, organ weights, hematologic findings, blood chemistry and tissue findings of the dogs.

Test Animals. Sprague-Dawley white rats, albino rabbits and mixed breed dogs.

Analytic and Test Procedures. After many preliminary experiments, it was decided to use ascending paper chromatography as the basic analytic procedure. The chromatographic solvent used most of the time was a butanol-acetic acid-water system (12-3-5), although other mixtures were used also. These generally gave satisfactory separations of the starting materials and the metabolic products. For the development of the chromatograms, the following were used most often; ultra-violet light, ninhydrin, Ehrlich's reagent and brom phenol blue.

Findings.

Acute Experiments. Single oral doses of the test solution were administered to each type of animal used. Urine was collected for ten days and examined for the test material and a variety of amino acids and other excretory products.

The findings in all animals were consistent, with some variation in the time factors due to the amount of test material ingested. Table 28 shows representative findings in the rabbit.

Generally, urine collected at about 4 hours after feeding one dose of the test material appeared to be deficient in urea, glycine and several other compounds, mainly the amino acids.

Six hours after feeding, urea was not detected in the urine and there were traces only of glycine and other amino acids.

After 24 hours, urea, glycine and some amino acids and related compounds were not detected in the urine, but ϵ -amino caproic acid was present.

The 46 hour urine indicated resumption of urea excretion. Glycine was still not detected. Free ϵ -caprolactam and ϵ -amino caproic acid were observed.

The 54 hour urine showed a normal urea content with glycine either very low or absent. Some of the amino acids were being excreted in greater than normal amounts. Unaltered ϵ -caprolactam was still present, as was ϵ -amino caproic acid.

Urine collected at 72 hours showed considerable amino-aciduria with amino acids of low R_f values predominant. Glycine was either very low or absent. ϵ -caprolactam and ϵ -amino caproic acid appeared in trace amounts.

Urines collected on the fifth day appeared normal except for the strong presence of an unidentified substance at R_f .17. No ϵ -caprolactam and no ϵ -amino caproic acid were detected.

Urines collected on the sixth and succeeding days showed normal chromatographic patterns.

Similar studies were performed after repeated daily doses of the test material. Representative findings are shown in Table 29, following 5 daily doses of the test material to rabbits.

Urea and glycine disappeared from the urine in the first 24 hours. Amino caproic acid appeared on the second day. Free ϵ -caprolactam appeared on the fourth day.

Amino caproic acid disappeared from the urine within 24 hours after the ingestion of the test material ceased. Free ϵ -caprolactam disappeared on the third day after ingestion ceased.

Urea and glycine reappeared in the urine within 24 hours after ingestion of the test material ceased.

Tissues were analyzed, also. With single oral doses, free E-caprolactam was found first in the liver, then as the dose was increased, in the kidneys, and finally in other organs. Likewise, E-amino caproic acid was found first in the liver and then in other organs.

With single intraperitoneal doses of the test material, no free E-caprolactam was found in the organs but E-amino caproic acid was present in the liver, kidney, heart and spleen.

Chronic Experiments. Urine was collected from animals which had been maintained on diets containing various amounts of the test material for 100 days. Representative findings are shown in Table 30 as compared with controls that received no test material.

Urea was present in the urines, showing that the depression in excretion noted in the acute experiments was of a temporary nature. E-caprolactam itself did not appear in the urine up to dosages of 167mg. per kg. of body weight. With larger doses, free E-caprolactam appeared in the urine. Amino caproic acid was present, although in the rats the amounts appeared to be small. Other constituents are shown in Table 30.

After withdrawal of the test material from the diet, animals receiving up to 167 mg. per kg. of body weight reverted to a normal urinary metabolite excretion pattern in one day, and those receiving greater amounts reverted to normal in two days. Thus there appeared to be no long term cumulative effect.

In Vitro Experiments. Tissue brei was prepared from the liver, kidney and other organs of normal animals. Part of the brei was used as a control and substrates of the test material were added to portions of the balance. Penicillin was added to prevent bacterial action. After incubation at 37 C. for varying periods of time, portions of the brei were analyzed by paper chromatography.

Incubation of liver tissue with the test material gave rise to E-amino caproic acid and at least one other metabolite of E-caprolactam. Kidney and other tissues had no such activity.

Conclusion. The liver appears to be the site of detoxification of E-caprolactam. On ingestion the compound first appears in the liver tissue before being found in other tissues. E-amino caproic acid and other metabolic products of E-caprolactam appear first in the liver. It is postulated that monoaminoxidase takes part in the deamination of some of the amino caproic acid, yielding the corresponding caproic acid.

Chronic Toxicity Studies in Rats.
Control Group
Body Weights in Grams (at intervals of approx. 100 days)

<u>Days</u> <u>Rats</u>	30	99	211	302	414	519	594	693	Final Wt.	Total days of Life
C1M	49	370	482	555	585	590	580	635	600	763
2*	48	358	427	451	470	484	495	-	505	639
3	51	324	400	448	473	493	495	500	510	765
4	65	340	470	540	575	592	615	620	600	762
5*	58	382	485	518	515	520	-	-	500	580
6	67	350	475	550	598	610	640	650	655	758
7	56	390	472	560	595	604	600	595	600	763
8	64	300	450	532	576	592	620	618	620	765
9	70	360	440	518	568	594	614	626	590	765
10	65	370	481	543	564	568	572	575	580	763

Avg. 8 male rats. *Excluded due to early death.

504	61	349	459	531	567	580	592	602	594	763
C11F	48	212	275	300	350	355	345	385	410	762
12	45	214	297	315	373	420	425	460	470	764
13	54	225	280	315	360	380	380	390	410	764
14	56	217	258	306	371	382	398	403	405	765
15	62	229	285	305	345	385	390	415	405	765
16	60	219	275	290	310	325	320	340	375	765
17	51	197	245	281	299	310	325	335	350	762
18	59	211	267	290	345	395	395	420	450	766
19	65	225	282	290	330	365	390	420	465	765
20	57	211	265	315	360	400	400	435	460	765

Avg. 10 female rats.

	56	216	273	301	344	372	377	400	420	764
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000108

Table 2.
Chronic Toxicity Studies in Rats
Control Group
Organ Weights in Grams

<u>Rat No.</u>	<u>Heart</u>	<u>Lungs</u>	<u>Liver</u>	<u>Kidneys</u>	<u>Spleen</u>	<u>Gonads</u>	<u>Final Body Weight</u>
C1M	2.0	3.4	16.6	3.6	0.9	5.1	600
2*	1.8	4.3	16.5	3.6	0.8	4.2	505
3	1.6	3.5	13.5	3.3	0.7	4.1	510
4	1.9	3.8	18.4	3.9	0.9	5.0	600
5*	1.6	4.0	15.5	3.2	0.9	3.0	500
6	2.1	3.9	18.6	3.9	0.66	3.7	655
7	1.9	3.6	17.0	3.5	0.8	3.8	600
8	2.0	3.5	19.7	3.6	0.8	3.5	620
9	1.9	3.8	17.0	4.1	1.0	3.2	590
10	1.8	3.9	14.7	3.9	0.9	3.4	580

Avg. 8 male rats. *Excluded due to early death.

	1.9	3.7	16.9	3.7	0.9	4.0	594
C11F	1.5	2.0	10.9	2.1	0.7	-	410
12	1.4	2.5	15.5	2.5	0.8	-	470
13	1.3	2.3	11.7	2.4	0.8	-	410
14	1.4	2.2	12.8	2.3	0.7	-	405
15	1.2	2.4	11.7	2.3	0.6	-	405
16	1.1	2.3	10.5	2.0	0.4	-	375
17	1.2	2.0	10.5	1.8	0.5	-	350
18	1.2	2.9	13.8	2.4	0.8	-	450
19	1.1	2.4	16.0	2.0	0.8	-	465
20	1.3	2.3	15.3	2.4	0.7	-	460

Avg. 10 female rats.

	1.3	2.3	12.9	2.2	0.7	-	420
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Table 4. ✓

Chronic Toxicity Studies in Rats
100 ug. Group
Body Weights in Grams (at intervals of approx. 100 days)

<u>Days</u> <u>Rate</u>	30	99	211	302	414	519	594	693	Final Wt.	Total days of Life
C21M	69	383	485	565	600	585	580	600	605	734
22	73	381	487	565	590	595	585	610	600	758
23	71	373	475	517	590	575	535	585	590	731
24*	76	362	466	570	615	480	420	-	385	643
25	79	375	490	580	615	595	560	580	545	758
26*	72	364	453	540	585	500	490	515	515	699
27	76	374	491	575	615	615	590	590	565	758
28	69	364	490	565	600	610	600	640	635	758
29	74	389	500	575	610	590	555	565	510	750
30	76	394	501	580	610	595	545	560	515	758

AVG. 8 male rats. *Excluded due to early death.

	74	379	490	565	604	595	569	591	570	751
C31F	59	263	318	350	390	400	375	385	405	763
32	69	210	297	335	355	380	355	365	375	763
33	55	228	275	295	340	375	360	370	390	763
34	64	219	245	290	320	340	325	345	390	763
35*	62	213	-	-	-	-	-	-	205	157
36	60	254	310	340	400	395	350	400	435	758
37	63	225	271	305	340	355	315	330	345	763
38*	57	222	258	310	565	-	-	-	565	414
39	59	212	288	320	395	385	365	380	405	763
40	60	210	255	295	345	365	335	360	390	763

AVG. 8 female rats. *Excluded due to early death.

	61	228	282	316	361	374	348	367	392	762
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000111

Chronic Toxicity Studies in Rats
100 mg. Group
Organ Weights in Grams

Rat No.	Heart	Lungs	Liver	Kidneys	Spleen	Gonads	Final Body Weight
C21M	2.1	3.9	19.9	4.2	1.1	4.8	605
22	1.7	3.5	18.8	3.7	1.1	5.2	600
23	1.8	4.2	16.6	3.8	1.2	5.0	590
24*	1.4	3.0	13.5	3.4	0.7	2.2	385
25	2.1	3.8	19.4	4.0	0.9	3.8	545
26*	2.0	4.1	17.0	3.8	1.0	3.7	515
27	1.8	4.1	19.6	3.8	1.0	4.7	565
28	1.9	3.4	21.8	3.8	1.1	3.2	635
29	2.0	3.5	17.0	3.5	0.5	3.1	510
30	1.8	3.6	16.2	3.5	0.7	4.0	515

Avg. 8 male rats. *Excluded due to early death.

	1.9	3.8	18.7	3.8	1.0	4.2	571
C31F	1.1	1.9	13.6	2.2	0.6	-	405
32	1.3	1.9	11.4	2.2	0.6	-	375
33	1.2	2.3	12.4	1.9	0.7	-	390
34	1.2	2.3	11.6	2.0	0.8	-	390
35*	-	-	-	-	-	-	205
36**	-	-	-	-	-	-	435
37	1.0	1.7	10.5	2.1	0.6	-	345
38*	1.1	1.9	9.9	2.1	0.5	-	565
39	1.1	1.9	11.5	2.0	0.5	-	405
40	1.2	2.2	11.9	2.3	0.6	-	390

Avg. 7 female rats. *Excluded due to early death.
**Excluded due to massive tumor.

	1.2	2.0	11.8	2.1	0.6	-	386
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Table 6.
Chronic Toxicity Studies in Rats
100 mg. Group
Summary of Body Weights, Longevity and
Clinical, Gross and Microscopic Pathology

Rat No.	Sex	Weight - grams			Age - days		Disposition	Clinical, Gross and Microscopic Pathology - Summary
		Start	Peak	Final	Peak Wt.	At End		
21	M	69	605	605	734	734	Sacr.	Ill 4 days. Sacrificed. Pneumonia*
22	M	73	625	600	730	758	Sacr.	None**
23	M	71	590	590	731	731	Died	Pneumonia*
24	M	76	630	385	380	643	Died	Pneumonia*
25	M	79	630	545	680	758	Sacr.	Slight chronic pyelonephritis. Otherwise none**
26	M	72	585	515	414	699	Died	Pleurisy, atelectasis, and a localized peritonitis.
27	M	76	630	565	680	758	Sacr.	Evidence of previous pneumonia* Otherwise none**
28	M	69	655	635	730	758	Sacr.	None**
29	M	74	620	510	380	750	Sacr.	Old inactive pyelonephritis. Hemosiderin in spleen. Otherwise none**
30	M	76	610	515	714	758	Sacr.	Evidence of previous pneumonia* Otherwise none**
31	F	59	410	405	656	763	Sacr.	Two benign tumors (fibroadenomas)*** Otherwise none**
32	F	69	380	375	719	763	Sacr.	None
33	F	55	390	390	763	763	Sacr.	None**
34	F	64	390	390	763	763	Sacr.	Benign tumor (fibroadenoma)*** Otherwise none**
35	F	62	228	205	141	157	Died	Pneumonia*
36	F	60	435	435	758	758	Sacr.	Benign tumor (fibroadenoma)*** Otherwise none**
37	F	63	355	345	719	763	Sacr.	Chronic pyelonephritis. Otherwise none**
38	F	57	565	565	414	414	Sacr.	Clinically ill. Sacrificed. Benign tumor (fibroadenoma)*** Pneumonia*
39	F	59	410	405	730	763	Sacr.	None**
40	F	60	390	390	763	763	Sacr.	None

* A common finding in rats of this age.

** The only changes noted were those consistent with age and dietary factors, none of which could be attributed to the ingested caprolactam.

*** Common in all breeds and strains of rats.

Chronic Toxicity Studies in Rats
500 mg. Group
Body Weights in Grams (at intervals of approx. 100 days)

<u>Days</u> <u>Rats</u>	30	99	211	302	414	519	594	693	Final Wt.	Total days of Life
C41M*	73	311	400	480	550	520	510	525	360	727
42	73	357	462	540	565	505	480	520	510	758
43	67	361	440	480	500	475	440	460	425	758
44	71	353	453	525	545	510	500	540	525	758
45	68	320	425	475	500	445	450	490	460	758
46**	74	380	455	510	540	485	445	445	275	758
47	72	347	440	500	500	480	315	440	405	759
48	74	358	420	500	530	510	500	520	500	759
49	69	356	440	490	490	465	440	475	450	759
50	73	365	453	525	540	505	460	475	400	752

Avg. 8 male rats. *Excluded due to early death.

**Excluded due to extreme emaciation.

	71	352	442	504	521	487	448	490	459	758
C51F*	63	223	285	295	315	345	315	-	263	603
52	68	229	285	300	305	295	285	320	295	762
53	56	217	267	285	295	305	295	315	320	762
54*	63	221	250	270	300	335	300	220	150	730
55	61	223	258	290	310	300	285	300	305	762
56	58	231	273	285	290	300	295	310	310	762
57	67	240	278	310	340	340	305	325	345	762
58	65	235	285	300	315	310	260	290	300	762
59	56	218	259	275	295	315	275	340	425	770
60	58	223	260	275	280	270	285	315	300	762

Avg. 8 female rats. *Excluded due to early death.

	61	227	271	290	304	304	286	314	325	763
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000114

Table 8.
Chronic Toxicity Studies in Rats
500 mg. Group
Organ Weights in Grams

<u>Rat No.</u>	<u>Heart</u>	<u>Lungs</u>	<u>Liver</u>	<u>Kidneys</u>	<u>Spleen</u>	<u>Gonads</u>	<u>Final Body Weight</u>
C41M*	1.5	2.8	12.6	3.0	0.8	-	360
42	1.9	2.9	16.1	4.3	0.9	4.2	510
43	1.6	2.9	13.1	3.1	1.0	3.7	425
44	2.2	3.8	18.2	4.2	1.2	2.9	525
45	1.5	2.3	13.1	3.1	1.0	3.9	460
46**	1.4	2.5	11.5	3.0	0.7	2.6	275
47	1.3	2.7	12.9	2.8	0.7	3.2	405
48	2.0	4.0	15.6	3.7	0.9	3.9	500
49	1.6	3.0	13.1	3.7	0.7	2.2	450
50	1.5	2.6	11.7	2.9	0.7	2.2	400

Avg. 8 male rats. *Excluded due to early death.

**Excluded due to extreme emaciation.

	1.7	3.0	14.5	3.5	0.9	3.3	459
C51F*	1.4	1.8	8.9	2.0	0.3	-	263
52	1.2	2.0	9.3	1.9	0.3	-	295
53	1.2	2.0	10.6	2.2	0.7	-	320
54*	1.0	2.0	5.9	1.7	0.4	-	150
55	1.2	2.2	9.2	2.1	0.6	-	305
56	1.1	1.9	10.3	1.8	0.7	-	310
57	1.3	2.3	12.6	2.4	0.7	-	345
58	1.0	1.9	10.6	2.0	0.6	-	300
59**	-	-	-	-	-	-	425
60	1.1	2.5	10.4	2.2	0.5	-	300

Avg. 7 female rats. *Excluded due to early death.

**Excluded due to massive tumor.

	1.2	2.3	10.4	2.1	0.6	-	311
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Table 9.
Chronic Toxicity Studies in Rats
500 mg. Group
Summary of Body Weights, Longevity and
Clinical, Gross and Microscopic Pathology

Rat No.	Sex	Weight - grams			Age - days		Disposition	Clinical, Gross and Microscopic Pathology - Summary
		Start	Peak	Final	Peak Wt.	At End		
041	M	73	555	360	456	727	Died	Lost weight over last month of life. Clinically weak. Died of pneumonia.
42	M	73	567	510	390	758	Sacr.	Focal necrosis of liver cells* Small areas of necrosis and nuclear changes in liver cells*. Hemosiderin in histiocytes of spleen. Anemia.
43	M	67	510	425	380	758	Sacr.	Evidence of previous pneumonia. Other changes consistent with old age.
44	M	71	555	525	380	758	Sacr.	Moderate glomerular nephritis. Hemosiderin in spleen. Marked anemia.
45	M	68	505	460	380	758	Sacr.	Subcutaneous cyst. Other changes consistent with old age.
46	M	74	540	275	414	758	Sacr.	Changes consistent with extreme emaciation.
47	M	72	510	405	380	759	Sacr.	Evidence of previous pneumonia. Other changes consistent with old age.
48	M	74	530	500	414	759	Sacr.	Changes consistent with old age.
49	M	69	490	450	414	759	Sacr.	Changes consistent with old age.
50	M	73	540	400	414	752	Died	Pneumonia. Moderate glomerular nephritis
51	F	63	350	263	561	603	Sacr.	Ill. Small areas of necrosis in liver* Moderate glomerular nephritis. Hemosiderin in spleen. Anemia. Perineal abscess.
52	F	68	325	295	661	762	Sacr.	Benign tumor (fibroadenoma)** Other changes consistent with old age.
53	F	56	320	320	762	762	Sacr.	Changes consistent with old age.
54	F	63	335	150	519	730	Died	Pneumonia. Changes consistent with extreme emaciation.
55	F	61	310	305	456	762	Sacr.	Focal necrosis of liver cells* Other changes consistent with old age.
56	F	58	310	310	762	762	Sacr.	Benign tumor (fibroadenoma)** Abscess in right ovary. Moderate glomerular nephritis. Changes of old age.
57	F	67	345	345	762	762	Sacr.	Two benign tumors (fibroadenomas)** Minimal necrosis of liver cells* Changes consistent with old age.
58	F	65	315	300	414	762	Sacr.	Cystic tumor in uterus (fibroma). Acute metritis. Minimal necrosis of liver cells* Changes of old age.
59	F	56	425	425	770	770	Sacr.	Benign tumor (fibroadenoma)** Old age.
60	F	58	315	300	693	762	Sacr.	Focal necrosis of liver cells* Moderate glomerular nephritis. Pneumonia. Old age.

* Consistent with toxic changes of chemical, infectious and/or metabolic origin.

** Common in all breeds and strains of rats.

000116

Chronic Toxicity Studies in Rats
1000 mg. Group
Body Weights in Grams (at intervals of approx. 100 days)

<u>Days</u> <u>Rats</u>	30	99	211	302	414	519	594	693	Final Wt.	Total days of Life
061M	74	349	421	460	425	408	375	335	290	757
62*	80	335	429	465	440	385	405	385	385	706
63*	72	318	385	420	-	-	-	-	430	402
64	79	340	420	435	420	370	380	415	320	757
65	71	320	375	425	445	420	410	395	300	757
66	72	330	433	480	390	335	275	280	230	757
67	74	320	400	430	420	365	370	430	370	758
68*	77	338	425	460	445	425	-	-	400	566
69*	72	305	370	410	405	365	355	-	315	678
70	75	306	415	445	420	395	380	325	310	758

AVG. 6 male rats. *Excluded due to early death.

	74	328	411	446	420	382	365	363	303	757
071F	61	199	245	260	260	270	265	255	245	759
72*	62	186	245	260	270	275	245	270	265	740
73	63	201	250	265	275	275	265	265	290	769
74	65	222	260	280	285	275	285	305	285	759
75	63	202	242	259	260	240	240	245	225	759
76	60	232	266	288	315	315	300	320	330	759
77	61	213	250	265	260	270	255	240	250	759
78	60	226	260	270	265	270	260	280	255	766
79*	56	199	238	270	280	265	255	270	270	714
80	57	208	252	260	270	260	245	260	265	766

AVG. 8 female rats. *Excluded due to early death.

	61	213	253	268	274	272	264	271	268	762
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Table 11.
Chronic Toxicity Studies in Rats
1000 mg. Group
Organ Weights in Grams

<u>Rat No.</u>	<u>Heart</u>	<u>Lungs</u>	<u>Liver</u>	<u>Kidneys</u>	<u>Spleen</u>	<u>Gonads</u>	<u>Final Body Weight</u>
C61M	1.1	2.2	10.2	2.5	0.7	2.0	290
62*	1.5	4.4	14.0	4.2	0.8	3.1	385
63*	2.5	4.8	20.4	5.6	1.3	-	430
64	1.3	2.2	10.6	2.3	0.9	1.7	320
65	1.4	2.5	9.0	1.9	0.6	2.4	300
66	0.9	1.5	7.0	1.6	0.7	1.8	230
67	1.7	2.7	13.1	3.1	0.9	2.7	370
68*	-	-	-	-	-	-	400
69*	1.4	2.7	15.0	2.6	0.7	-	315
70	1.2	2.4	12.2	2.5	0.9	2.1	310

Avg. 6 male rats. *Excluded due to early death.

	1.3	2.3	10.3	2.3	0.8	2.1	303
C71F	0.9	2.1	10.0	1.9	0.4	-	245
72*	1.0	3.1	14.0	2.2	0.4	-	265
73	1.1	2.0	10.0	2.2	0.7	-	290
74	1.1	2.3	10.7	2.0	0.7	-	285
75	1.0	1.9	8.8	1.6	0.5	-	225
76	1.2	2.1	11.5	2.2	0.6	-	330
77	1.0	1.8	8.7	1.6	0.5	-	250
78	1.1	1.9	8.1	2.1	0.5	-	255
79*	1.3	2.8	12.5	1.9	0.6	-	270
80	1.1	1.7	11.0	2.0	0.7	-	265

Avg. 8 female rats. *Excluded due to early death.

	1.1	2.0	9.9	1.9	0.6	-	268
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000118

Chronic Toxicity Studies in Rats
1000 mg. Group
Summary of Body Weights, Longevity and
Clinical, Gross and Microscopic Pathology

Rat No.	Sex	Weight - grams			Age - days		Disposition	Clinical, Gross and Microscopic Pathology - Summary
		Start	Peak	Final	Peak Wt.	At End		
661	M	74	465	290	272	757	Sacr.	Emaciated and debilitated. Anemia. Hemosiderin in spleen. Emphysema and hyperemia of lung. Liver and kidneys show necrosis* Remnants, only, of seminiferous tubules renal
62	M	80	465	385	380	706	Died	Multiple abscessed fibromas. Kidneys and liver show necrosis* Septicemic
63	M	72	430	430	380	402	Sacr.	Ill. Liver, spleen and kidneys show necrosis*
64	M	79	440	320	272	757	Sacr.	Emaciated and weak. Congestion and toxic degeneration in kidneys.
65	M	71	465	300	380	757	Sacr.	Emaciated. Two benign fibromas, one abscessed. Liver shows necrosis* Healed previous pyelonephritis.
66	M	72	480	230	302	757	Sacr.	Extreme emaciation. Some slight posterior paralysis. Liver necrosis
67	M	74	440	370	272	758	Sacr.	Liver, spleen and kidneys show necrosis, altho minimal*
68	M	77	460	400	302	566	Died	Diarrhea. Postmortem degeneration prevented further diagnosis.
69	M	72	415	315	380	678	Died	Emaciated. Liver, kidneys and spleen show necrosis* Pneumonia. Testicle atrophied.
70	M	75	445	310	302	758	Sacr.	Liver, spleen and kidneys show necrosi
71	F	61	270	245	661	759	Sacr.	Liver and kidneys show minimal necrosi
72	F	62	275	265	519	740	Died	Pneumonia. Benign tumor (fibroadenoma) Liver and kidneys show minimal necrosis*
73	F	63	290	290	769	769	Sacr.	Benign tumor (fibroadenoma)** Liver and kidneys show minimal necrosis* Hemosiderin in spleen. Emphysema.
74	F	65	305	285	693	759	Sacr.	Liver and kidneys show minimal necrosi Cyst on left ovary.
75	F	63	265	225	380	759	Sacr.	Liver and kidneys show necrosis* Cyst on right horn of ovary.
76	F	60	345	330	730	759	Sacr.	Small areas of focal necrosis in liver Hemosiderin in spleen. Atelectasis of lung.
77	F	61	270	250	730	759	Sacr.	Liver and kidneys show minimal necrosi Uterine wall thick and fibroid.
78	F	60	280	255	693	766	Sacr.	Liver and kidneys show minimal necrosi Uterine wall thickened.
79	F	56	290	270	661	714	Died	Pneumonia.
80	F	57	280	265	730	766	Sacr.	Liver and kidneys show minimal necrosis Cystic uterus.

* Consistent with toxic changes of chemical, infectious and/or metabolic origin.

** Common in all breeds and strains of rats.

000119

Table 13.
Chronic Toxicity Studies in Rats
Control Group
Organ Weights in Grams/100 gm. of Body Weight

<u>Rat No.</u>	<u>Body Wt.</u>	<u>Heart</u>	<u>Lungs</u>	<u>Liver</u>	<u>Kidneys</u>	<u>Spleen</u>	<u>Gonads</u>
C1M	600	0.33	0.57	2.77	0.60	0.15	0.85
3	510	0.31	0.69	2.65	0.65	0.14	0.80
4	600	0.32	0.63	3.07	0.65	0.15	0.83
6	655	0.32	0.60	2.84	0.60	0.09	0.57
7	600	0.32	0.60	2.83	0.58	0.13	0.63
8	620	0.32	0.56	3.18	0.58	0.13	0.56
9	590	0.32	0.64	2.88	0.69	0.17	0.54
10	580	0.31	0.67	2.53	0.67	0.16	0.59
Mean	594	0.32	0.62	2.84	0.63	0.14	0.67
Std.E*	<u>±14</u>	<u>±0.002</u>	<u>±0.02</u>	<u>±0.07</u>	<u>±0.02</u>	<u>±0.01</u>	<u>±0.05</u>
C11F	410	0.37	0.49	2.66	0.51	0.17	-
12	470	0.30	0.53	3.30	0.53	0.17	-
13	410	0.32	0.56	2.85	0.59	0.20	-
14	405	0.35	0.54	3.16	0.57	0.17	-
15	405	0.30	0.59	2.89	0.57	0.15	-
16	375	0.29	0.61	2.80	0.53	0.11	-
17	350	0.34	0.57	3.00	0.51	0.14	-
18	450	0.27	0.64	3.07	0.53	0.18	-
19	465	0.24	0.52	3.44	0.43	0.17	-
20	460	0.28	0.50	3.32	0.52	0.15	-
Mean	420	0.31	0.55	3.05	0.53	0.16	-
Std.E*	<u>±13</u>	<u>±0.001</u>	<u>±0.02</u>	<u>±0.08</u>	<u>±0.01</u>	<u>±0.01</u>	-

* Standard error of mean

000120

Table 14.
Chronic Toxicity Studies in Rats
100 mg. Group
Organ Weights in Grams/100 gm. of Body Weight

<u>Rat No.</u>	<u>Body Wt.</u>	<u>Heart</u>	<u>Lungs</u>	<u>Liver</u>	<u>Kidneys</u>	<u>Spleen</u>	<u>Gonads</u>
C21M	605	0.35	0.65	3.29	0.70	0.18	0.79
22	600	0.28	0.58	3.13	0.62	0.18	0.87
23	590	0.31	0.71	2.81	0.64	0.20	0.85
25	545	0.38	0.70	3.56	0.73	0.16	0.70
27	565	0.32	0.73	3.47	0.67	0.18	0.83
28	635	0.30	0.54	3.43	0.60	0.17	0.50
29	510	0.39	0.68	3.33	0.69	0.10	0.61
30	515	0.35	0.70	3.15	0.68	0.14	0.78
Mean	571	0.34	0.66	3.27	0.67	0.16	0.74
Std.E*	<u>+16</u>	<u>+0.01</u>	<u>+0.02</u>	<u>+0.08</u>	<u>+0.02</u>	<u>+0.01</u>	<u>+0.05</u>
C31F	405	0.27	0.47	3.36	0.54	0.15	-
32	375	0.35	0.51	3.04	0.59	0.16	-
33	390	0.31	0.59	3.18	0.49	0.18	-
34	390	0.31	0.59	2.97	0.51	0.21	-
37	345	0.29	0.49	3.04	0.61	0.17	-
39	405	0.27	0.47	2.84	0.49	0.12	-
40	390	0.31	0.51	3.05	0.59	0.15	-
Mean	386	0.30	0.52	3.07	0.55	0.16	-
Std.E*	<u>+ 8</u>	<u>+0.01</u>	<u>+0.02</u>	<u>+0.06</u>	<u>+0.02</u>	<u>+0.01</u>	-

* Standard error of mean

000121

Table 15.
 Chronic Toxicity Studies in Rats
 500 mg. Group
Organ Weights in Grams/100 gm. of Body Weight

<u>Rat No.</u>	<u>Body Wt.</u>	<u>Heart</u>	<u>Lungs</u>	<u>Liver</u>	<u>Kidneys</u>	<u>Spleen</u>	<u>Gonads</u>
C42M	510	0.37	0.57	3.57	0.84	0.16	0.82
43	425	0.37	0.68	3.08	0.73	0.24	0.87
44	525	0.42	0.72	3.46	0.80	0.23	0.55
45	460	0.33	0.50	2.85	0.68	0.22	0.85
47	405	0.32	0.66	3.18	0.69	0.17	0.79
48	500	0.40	0.80	3.12	0.74	0.18	0.78
49	450	0.35	0.67	2.91	0.82	0.15	0.49
50	400	0.38	0.65	2.93	0.73	0.18	0.55
Mean	459	0.37	0.66	3.14	0.75	0.19	0.71
Std.E*	± 17	± 0.01	± 0.03	± 0.09	± 0.02	± 0.01	± 0.05
C52F	295	0.41	0.68	3.15	0.64	0.18	-
53	320	0.37	0.63	3.31	0.69	0.22	-
55	305	0.39	0.72	3.02	0.69	0.20	-
56	310	0.35	0.61	3.32	0.58	0.22	-
57	345	0.38	0.67	3.65	0.70	0.20	-
58	300	0.33	0.63	3.53	0.67	0.20	-
60	300	0.37	0.83	3.47	0.73	0.17	-
Mean	311	0.37	0.68	3.35	0.67	0.20	-
Std.E*	± 6	± 0.01	± 0.03	± 0.08	± 0.02	± 0.01	-

* Standard error of mean

CHRONIC TOXICITY STUDIES IN RATS
 1000 mg. Group
Organ Weights in Grams/100 gm. of Body Weight

<u>Rat No.</u>	<u>Body Wt.</u>	<u>Heart</u>	<u>Lungs</u>	<u>Liver</u>	<u>Kidneys</u>	<u>Spleen</u>	<u>Gonads</u>
C61M	290	0.38	0.76	3.54	0.86	0.24	0.69
64	320	0.41	0.69	3.33	0.72	0.28	0.53
65	300	0.47	0.83	3.00	0.63	0.20	0.80
66	230	0.39	0.65	3.04	0.70	0.30	0.78
67	370	0.46	0.73	3.54	0.84	0.24	0.73
70	310	0.39	0.77	3.94	0.81	0.29	0.68
Mean	303	0.42	0.74	3.40	0.76	0.26	0.70
Std.E*	<u>+18</u>	<u>+0.02</u>	<u>+0.03</u>	<u>+0.14</u>	<u>+0.04</u>	<u>+0.02</u>	<u>+0.04</u>
C71F	245	0.37	0.85	4.08	0.78	0.16	-
73	290	0.38	0.69	3.45	0.76	0.24	-
74	285	0.39	0.81	3.75	0.70	0.25	-
75	225	0.44	0.84	3.91	0.71	0.22	-
76	330	0.36	0.64	3.49	0.67	0.18	-
77	250	0.40	0.72	3.47	0.64	0.20	-
78	255	0.43	0.75	3.17	0.82	0.20	-
80	265	0.41	0.64	4.15	0.75	0.26	-
Mean	268	0.40	0.74	3.68	0.73	0.21	-
Std.E*	<u>+11</u>	<u>+0.01</u>	<u>+0.03</u>	<u>+0.12</u>	<u>+0.02</u>	<u>+0.01</u>	-

* Standard error of mean

000123

Table 17.
Chronic Toxicity Studies in Rats
Summary of Body and Organ Weights

Dosage , mg/kg/ day	Body Wt. Mean±SE* gm.	Organ Weights (wet) in Grams/100 gm. of Body Wt. (Mean ± SE*)						
		Heart	Lungs	Liver	Kidneys	Spleen	Gonads	
MALES								
Controls	594 ± 14	0.32 ± 0.002	0.62 ± 0.02	2.84 ± 0.07	0.63 ± 0.02	0.14 ± 0.01	0.67 ± 0.05	
100	571 ± 16	0.34 ± 0.01	0.66 ± 0.02	3.27 ± 0.08	0.67 ± 0.02	0.16 ± 0.01	0.74 ± 0.05	
→ 500	459 ± 17	0.37 ± 0.01	0.66 ± 0.03	3.14 ± 0.09	0.75 ± 0.02	0.19 ± 0.01	0.71 ± 0.05	
→ 1000	303 ± 18	0.42 ± 0.02	0.74 ± 0.03	3.40 ± 0.14	0.76 ± 0.04	0.26 ± 0.02	0.70 ± 0.04	
FEMALES								
Controls	420 ± 13	0.31 ± 0.001	0.55 ± 0.02	3.05 ± 0.08	0.53 ± 0.01	0.16 ± 0.01	-	
100	386 ± 8	0.30 ± 0.01	0.52 ± 0.02	3.07 ± 0.06	0.55 ± 0.02	0.16 ± 0.01	-	
500	311 ± 6	0.37 ± 0.01	0.68 ± 0.03	3.35 ± 0.08	0.67 ± 0.02	0.20 ± 0.01	-	
1000	268 ± 11	0.40 ± 0.01	0.74 ± 0.03	3.68 ± 0.12	0.73 ± 0.02	0.21 ± 0.01	-	

* Standard error of mean.

Table 18.
Chronic Toxicity Studies in Rats
Summary of Pathology

Group mg/kg/day	Sex	No. Rats	No. Died	Immediate Cause of Death			No. Sacr.	Pathology	
				Pneu(1)	Peri(2)	Sept(3)		None(5)	Fibro(6)
Controls	M	10	2	-	-	-	8	10	-
100	M	10	3	1	-	-	7	10	-
500	M	10	2	-	-	-	8	5	5
1000	M	10	3	-	1	1	7	-	10
Controls	F	10	-	-	-	-	10	10	4
100	F	10	1	-	-	-	9	10	4
500	F	10	1	-	-	-	9	4	4
1000	F	10	2	-	-	-	8	-	2

- (1) Pneumonia
- (2) Peritonitis
- (3) Septicemia
- (4) Unknown

(5) No pathology or pathology not related directly to the test material, such as the tissue changes due to old age.

(6) Fibroadenomas, not related to the ingestion of the test material.

(7) Signs of toxic degeneration in one or more tissues.

Table 19.
 Chronic Toxicity Studies in Rats
 Summary of Hematologic Findings
 (Rats with pneumonia and acute clinical conditions excluded)

Males	Age months	No. Rats	Hemoglob. gm/100ml.	Leukocytes $10^3/mm^3$	Morphology*	Bone Marrow**
Controls	6	10	13.8	12.8	Normal	
	12	10	14.7	13.1	Normal	
	18	9	14.9	12.6	Normal	
	24	7	14.2	14.3	Normal	Normal
100 mg.	6	10	14.2	13.2	Normal	
	12	10	14.9	14.1	Normal	
	18	10	14.6	14.2	Normal	
	24	7	14.6	14.2	Normal	Normal
500 mg.	6	10	14.3	12.6	Normal	
	12	10	15.0	14.5	Normal	
	18	10	14.2	15.8	Normal	
	24	7	12.1	16.1	Sl. anemia	Normal
1000 mg.	6	10	14.1	11.8	Normal	
	12	10	14.7	13.2	Normal	
	18	9	12.1	14.2	Sl. anemia	
	24	6	8.3	16.5	Marked anemia Increased neutrophils	Increased myeloid cells

* Normal mean: 25 to 33% neutrophils, 65 to 70% lymphocytes, 2 to 3% others.

** Normal mean: 65 to 70% myeloid cells, 30 to 35% erythroid cells.

Table 19 continued on next sheet.

Table 19 concluded.
 Chronic Toxicity Studies in Rats
 Summary of Hematologic Findings
 (Rats with pneumonia and acute clinical conditions excluded)

Females	Age months	No. Rats	Hemoglob. gm/100ml.	Leukocytes $10^3/mm^3$	Morphology*	Bone Marrow**
Controls	6	10	14.2	13.4	Normal	
	12	10	14.9	13.9	Normal	
	18	10	13.9	13.8	Normal	
	24	10	13.9	13.8	Normal	Normal
100 mg.	6	9	13.8	14.2	Normal	
	12	9	14.6	13.8	Normal	
	18	8	14.7	13.9	Normal	
	24	8	14.0	13.9	Normal	Normal
500 mg.	6	10	13.6	13.9	Normal	
	12	10	14.4	14.2	Normal	
	18	10	13.2	14.4	Normal	
	24	7	11.8	15.2	Sl. anemia	Normal
1000 mg.	6	10	14.0	14.1	Normal	
	12	10	14.8	15.1	Normal	
	18	10	12.7	15.4	Normal	
	24	8	10.8	15.8	Marked anemia Increased neutrophils	Increased myeloid cells

* Normal mean: 25 to 33% neutrophils, 65 to 70% lymphocytes, 2 to 3% others.

** Normal mean: 65 to 70% myeloid cells, 30 to 35% erythroid cells.

Table 20.
 Reproduction Studies in Rats
 Summary of Findings

	First Generation			Second Generation			Third Generation											
	Control Breeding			Control Breeding			Control Breeding											
	1	2	3	1	2	3	1	2	3									
No. females bred	20	18	17	20	19	19	20	20	19	20	20	18	18					
No. litters born	18*	17**	17	19**	17*	17	19**	19	18	20	18***18	18**	18**18	17**				
No. pups born	190	192	187	186	200	185	188	205	190	228	189	194	244	180	176	160	187	185
Avg. pups/litter	10.6	11.3	11.0	9.8	11.8	10.9	9.9	10.8	10.6	11.4	10.5	10.8	12.2	10.0	9.8	8.9	10.4	10.6
Pups born that survived more than one day.	142	150	135	149	164	142	150	151	146	164	153	145	157	129	139	125	155	154
Per cent pups born that survived more than one day	75	78	72	80	82	77	80	74	77	72	81	75	64	72	79	78	83	83
Pups that were weaned	116	127	108	116	133	118	108	118	118	138	112	107	140	102	114	100	121	119
Percent pups surviving more than one day that were weaned	82	85	80	78	81	83	72	78	81	84	73	74	90	79	82	80	78	77

* One died of uterine hemorrhage and one of pneumonia.
 ** One died of pneumonia.
 *** Two died of pneumonia.
 # One litter all born dead and not included. One died of pneumonia.
 ## One rat did not become pregnant.

Table 21.
 Chronic Toxicity Studies in Dogs
 Body Weights in Kg. (at intervals of 12 weeks)

Dog No.	Sex	Dosage mg/kg/day	Start	Weeks									
				12	24	36	48	60	72	84	96	108	122
1	M	0	6.4	6.8	7.3	7.7	7.7	8.0	8.1	8.5	8.7	9.0	9.0
2	F	0	11.8	12.7	14.0	14.9	15.3	15.6	16.0	11.0	-	-	-
3	M	100	14.2	14.0	13.8	14.5	14.9	15.2	15.5	15.7	16.1	16.5	16.7
4	F	100	9.5	10.0	10.3	10.6	11.2	11.5	11.9	7.8	-	-	-
5	M	250	15.1	16.4	17.8	19.1	19.2	20.0	20.4	19.6	19.8	20.3	20.7
6	M	500	5.4	5.8	5.5	6.1	6.3	6.5	6.4	6.2	6.7	6.2	6.3
7	F	500	8.7	9.1	9.3	9.6	10.0	10.3	10.5	10.4	9.6	9.0	7.5
8	F	750	11.8	11.0	10.5	11.4	11.8	12.4	12.3	11.9	11.0	10.8	10.5
9	M	1000	15.5	14.3	14.0	14.4	14.7	14.6	14.5	13.5	13.8	13.1	12.4
10	F	1000	8.1	7.5	8.2	8.3	8.9	9.0	8.8	8.6	8.0	7.0	5.7

Table 22.
 Chronic Toxicity Studies in Dogs
Per Cent Change in Body Weight (at intervals of 12 weeks)

Dog No.	Sex	Dosage mg/kg/day	Start	Weeks									
				12	24	36	48	60	72	84	96	108	122
1	M	0	100	106	114	120	120	125	127	133	136	141	141
2	F	0	100	108	119	126	130	132	136	93	-	-	-
3	M	100	100	99	97	102	105	107	109	111	113	116	118
4	F	100	100	105	108	112	118	121	125	82	-	-	-
5	M	250	100	109	118	127	127	132	135	130	131	134	137
6	M	500	100	107	102	113	117	120	119	115	124	115	117
7	F	500	100	105	107	110	115	118	121	120	110	104	86
8	F	750	100	98	89	97	100	105	104	101	93	91	89
9	M	1000	100	92	90	93	95	94	94	87	89	84	80
10	F	1000	100	93	101	102	110	111	109	106	99	86	70

Table 23.
Chronic Toxicity Studies in Dogs
Organ Weights in Grams

Dog No.	Sex	Dosage mg/kg/day	Heart	Lungs	Liver	Kidneys	Spleen	Gonads	Pancreas	Body Wt. kg.
1.	M	0	71	55	260	50	24	20	36	9.0
2	F	0	95	68	308	55	33	1.1	42	11.0
3	M	100	142	99	482	85	50	43	53	16.7
4	F	100	67	42	230	46	27	0.8	32	7.8
5	M	250	163	135	551	113	58	40	80	20.7
6	M	500	54	44	184	38	21	14	30	6.3
7	F	500	68	51	241	43	28	0.8	28	7.5
8	F	750	92	99	343	71	43	1.1	43	10.5
9	M	1000	99	113	453	87	56	27	54	12.4
10	F	1000	52	46	200	42	23	0.7	21	5.7

000131

Table 24.
 Chronic Toxicity Studies in Dogs
Organ Weights in Grams/100 gm. of Body Weight

Dog No.	Sex	Dosage mg/ka/day	Heart	Lungs	Liver	Kidneys	Spleen	Gonads	Pancreas	Body Wt. kg.
1	M	0	0.79	0.61	3.11	0.55	0.27	0.22	0.40	9.0
2	F	0	0.86	0.62	2.80	0.50	0.30	0.01	0.38	11.0
3	M	100	0.85	0.59	2.88	0.51	0.30	0.26	0.32	16.7
4	F	100	0.86	0.54	2.95	0.59	0.35	0.01	0.41	7.8
5	M	250	0.79	0.65	2.66	0.54	0.28	0.19	0.39	20.7
6	M	500	0.86	0.70	2.92	0.61	0.33	0.22	0.48	6.3
7	F	500	0.91	0.68	3.21	0.57	0.37	0.01	0.37	7.5
8	F	750	0.88	0.94	3.27	0.68	0.41	0.01	0.41	10.5
9	M	1000	0.80	0.91	3.65	0.70	0.45	0.22	0.44	12.4
10	F	1000	0.91	0.81	3.50	0.74	0.40	0.01	0.37	5.7

000132

Table 25.
 Chronic Toxicity Studies in Dogs
 Summary of Hematologic Findings

Dog	Sex	Dosage mg/kg/day	Time no.	Hb g/ 100ml	Leuk ₃ 10 ³ / mm	Diff. Count (%)					Bone Marrow
						N	L	M	E	B	
1	M	0	0	14.5	11.4	68	29	0	3	0	-
			6	14.6	10.1	65	30	1	4	0	-
			12	15.1	12.4	68	28	0	4	0	-
			18	14.8	13.2	70	25	2	3	0	-
			24	14.7	12.7	65	30	1	4	0	Normal
2	F	0	0	13.0	12.4	62	34	0	4	0	-
			6	13.4	12.2	60	35	0	5	0	-
			12	14.2	14.0	68	27	1	4	0	-
			18	12.6	16.4	72	25	1	2	0	Very slight granulocytic hyperplasia
			24	-	-	-	-	-	-	-	-
3	M	100	0	14.5	11.8	72	25	0	3	0	-
			6	15.1	12.1	71	24	0	5	0	-
			12	14.8	10.6	68	29	0	3	0	-
			18	14.7	10.8	65	30	1	4	0	-
			24	15.2	11.3	67	28	1	4	0	Normal
4	F	100	0	13.8	11.4	72	24	0	2	0	-
			6	14.2	10.8	77	18	1	4	0	-
			12	14.5	12.7	70	24	1	5	0	-
			18	12.9	15.3	74	21	1	4	0	Normal
			24	-	-	-	-	-	-	-	-
5	M	250	0	15.4	9.4	68	26	2	4	0	-
			6	14.8	9.7	65	33	0	2	0	-
			12	15.2	10.4	70	26	1	3	0	-
			18	15.4	10.4	72	25	1	2	0	-
			24	14.9	11.3	68	28	0	4	0	Normal

Table 25 concluded on next sheet.

Table 25 concluded.
 Chronic Toxicity Studies in Dogs
 Summary of Hematologic Findings

Dog	Sex	Dosage ng/kg/day	Time mo.	Hb gm/ 100ml	Leuqs 10 ³ / mm ³	Diff. Count (%)					Bone Marrow
						N	L	M	E	B	
6	M	500	0	15.2	12.7	71	26	0	3	0	-
			6	15.0	12.0	68	27	1	4	0	-
			12	14.7	10.4	74	23	0	3	0	-
			18	14.0	12.2	72	25	1	2	0	-
			24	12.8	14.5	77	20	1	2	0	Normal
7	F	500	0	14.4	13.2	65	30	1	4	0	-
			6	14.6	11.8	68	29	1	2	0	-
			12	14.9	12.5	73	22	2	3	0	-
			18	14.8	11.9	70	25	1	4	0	-
			24	13.8	12.2	72	22	1	5	0	Very slight erythro- blastic hyperplasia
8	F	750	0	14.0	13.4	64	31	0	5	0	-
			6	15.2	10.6	68	29	1	2	0	-
			12	14.7	10.6	65	30	2	3	0	-
			18	13.2	11.0	71	25	0	4	0	-
			24	11.5	12.8	70	25	1	4	0	Slight erythroblastic hyperplasia
9	M	1,000	0	15.4	10.2	65	33	0	2	0	-
			6	15.0	10.4	66	32	0	2	0	-
			12	14.2	12.3	71	25	1	3	0	-
			18	12.7	13.8	68	25	2	5	0	-
			24	10.5	13.7	77	14	4	5	0	Slight erythroblastic hyperplasia
10	F	1,000	0	14.6	11.4	70	24	1	5	0	-
			6	15.2	11.9	65	29	0	6	0	-
			12	14.5	11.0	68	27	1	4	0	-
			18	13.1	12.5	72	24	2	2	0	-
			24	10.8	14.4	60	15	1	4	0	Slight erythroblastic hyperplasia

Table 26.
 Chronic Toxicity Studies in Dogs
 Summary of Blood Chemistry Findings

Dog	Sex	Dosage mg/kg/day	Time mo.	Glucose mg/100ml	Urea N mg/100ml	Protein per cent
1	M	0	0	84	11.2	6.2
			6	88	11.4	6.5
			12	90	11.3	6.6
			18	85	11.3	6.1
			24	86	11.5	6.1
2	F	0	0	80	12.0	6.8
			6	84	11.8	6.9
			12	85	12.4	6.8
			18	80	12.5	6.6
			24	-	-	-
3	M	100	0	75	12.1	6.4
			6	80	12.2	6.8
			12	84	13.0	7.1
			18	78	12.5	6.7
			24	77	12.5	6.7
4	F	100	0	78	10.8	7.2
			6	80	11.4	7.1
			12	80	12.0	7.4
			18	75	11.7	7.2
			24	-	-	-
5	M	250	0	70	12.8	6.9
			6	74	12.4	7.1
			12	75	11.9	7.1
			18	74	12.2	6.8
			24	80	12.4	6.4

Table 26 continued on next sheet.

Table 26 continued
Chronic Toxicity Studies in Dogs
Summary of Blood Chemistry Findings

Dog	Sex	Dosage mg/kg/day	Time mo.	Glucose mg/100ml	Urea N mg/100ml	Protein per cent
6	M	500	0	82	11.7	7.2
			6	80	11.6	6.7
			12	79	12.0	6.5
			18	84	12.1	6.8
			24	80	12.0	7.1
7	F	500	0	80	12.1	6.8
			6	75	12.4	6.9
			12	82	11.9	6.9
			18	83	12.2	6.5
			24	75	12.5	6.0
8	F	750	0	77	12.4	7.6
			6	78	11.8	7.5
			12	80	11.9	7.7
			18	75	12.5	7.0
			24	72	14.2	6.8
9	M	1,000	0	84	11.8	6.2
			6	82	12.5	6.4
			12	85	12.5	6.3
			18	80	12.8	6.0
			24	72	16.8	5.4
10	F	1,000	0	78	12.5	7.4
			6	78	12.7	7.2
			12	85	12.6	7.2
			18	80	13.4	6.5
			24	70	18.2	5.1

Table 27.
Chronic Toxicity Studies in Dogs
Summary of Pathology

<u>Dog</u>	<u>Sex</u>	<u>Dosage mg/kg/day</u>	<u>Immediate Cause of death</u>	<u>Pathology Present</u>
1	M	0	Sacrifice	No pathology
2	F	0	Pneumonia	Pneumonia, septicemia and endocarditis
3	M	100	Sacrifice	No pathology
4	F	100	Pneumonia	Pneumonia
5	M	250	Sacrifice	No pathology
6	M	500	Sacrifice	Slight inflammation in parenchymal cells of liver
7	F	500	Sacrifice	A few focal areas of degeneration in the liver infiltrated with phago- cytic cells. Some inflammation in parenchymal cells.
8	F	750	Sacrifice	Small foci of degeneration in liver, deposits of blood pigment. Kidney showed cloudy swelling.
9	M	1,000	Sacrifice	Degeneration of cord and parenchymal cells in liver with blood pigment. Kidney shows degeneration of glomeruli and tubules. Spleen hemochromatosis.
10	F	1,000	Sacrifice	Degeneration of cord and parenchymal cells in liver with blood pigment. Kidney shows degeneration of glomeruli and tubules. Spleen hemochromatosis. Cloudy swelling around islet cells in pancreas.

Table 28.
Metabolic Studies
Urine Findings in the Rabbit after One Oral Dose* of Test Solution
as determined by chromatographic studies

Hour	Urea	Glycine	Various Amino Acids Related compounds	Free E-Capro- lactam	E-Amino-capro- ic Acid
0	Normal	Normal	Normal	Absent	Absent
4	Low	Low	Low	Absent	Absent
6	Absent	Trace	Trace	Absent	Absent
24	Absent	Absent	Low	Absent	Present
46	Low	Absent	Low	Present	Present
54	Normal	Low or absent	High	Present	Present
72	Normal	Low or absent	High	Trace	Trace
96	Normal	Normal	Normal	Absent	Absent

* 1,000 mg. per kg. of body weight.

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Metabolic Studies
 Urine Findings in the Rabbit after Five Daily Oral Doses of Test Material
 as determined by chromatographic studies

Day	Dose mg/kg/day	R _f Values of Excretion Products								
		.06	.10	.15	.23	.28	.30	.41	.46	.92
0	0		X	X	X	X			X	
1	500	X	X							
2	500	X	X	X		X		X		
3	500	X		X	X	X	X	X		
4	500	X	X	X	X		X	X		X
5	500	X	X	X	X		X	X		X
6	0	X	X	X		X	X		X	X
7	0	X	X	X			X		X	X
8	0		X	X	X		X		X	
9	0		X	X	X				X	
10	0		X	X	X		X		X	
11	0		X	X	X		X		X	
12	0		X	X	X		X		X	
13	0		X	X	X		X		X	
14	0		X	X	X		X		X	
15	0		X	X	X		X		X	

X - positive.

R_f .06 - unidentified metabolite of the test material.

R_f .10 to .30 - various amino acids, related compounds, glycine and reducing sugars.

R_f .41 - L-amino caproic acid.

R_f .46 - urea.

R_f .92 - L-Caprolactam.

Table 30.
Metabolic Studies.
Urine Findings in Rats Following 100 Days of Daily Oral Doses of Test Material
as determined by chromatographic studies

Daily Dose mg./kg.	R _f Values of Urine Excretory Products										
	A	B	C	D	E	F	G	H	I	J	
0	.07	.14	.25	.30	.34		.46		.68		
5	.06	.13	.23	.30	.35		.46		.67		
44		.12	.27	.30	.36	.41	.46	.50	.67		
88		.11		.30		.40	.46	.50			
167	.07	.13	.24	.30	.36	.41	.44		.70		
333	.07	.15	.25	.30	.36	.41	.45		.71	.82	
666	.06	.14	.22	.30	.35	.40	.44		.69	.83	
E-Capro- lactam										.82	

- A, B, C - Guanidine compounds (arginine, creatine, etc.) and glycine.
- D, H - Reducing type compounds (reducing sugars).
- E - Alanine.
- F - E-Aminocaproic acid.
- G - Urea
- I - Leucine.
- J - E-Caprolactam.

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