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FOUR-WEEK ORAL TOXICITY STUDY OF 4-METHYLCYCLOHEXANE METHANOL IN THE RAT

HAEL NO. 89-0081 ACC. NO. 907670

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Abstract

Groups of two male and two female rats were given doses of 200, 400, or 800 mg/kg/day of 4-methylcyclohexane methanol in corn oil for five days as part of a probe study conducted to establish dose levels for the four-week toxicity study. Rats dosed with 800 mg/kg showed signs of narcosis resulting in decreased activity levels (one male and two females) and ataxia (one female). One of the female rats was subsequently euthanatized. One of the 400 mg/kg/day females had decreased activity on Days 2 and 3 of the study. The remaining animals did not exhibit clinical abnormalities related to exposure to the test article. Dose levels of 0, 25, 100, and 400 mg/kg/day were chosen for the four-week study based on these results.

In the four-week study, the test article was administered five days per week by gavage in corn oil to groups of five male and five female rats. No mortality was observed during this study. Minimal reductions in body weight growth were present for both male and female rats given the high-dose of the test article. These differences were not statistically significant. At lower dose levels, no consistent effect was noted. Males given the lower doses weighed slightly less than their control group while females weighed slightly more. Feed consumption was unaffected by administration of the test material.

Sialorrhea after dose administration occurred frequently in the 400 mg/kg male and female dose groups from Days 14 to 28. Transient depression of activity occurred in one 400 mg/kg female animal on Day 3 of the study. These were the only two treatment-related clinical observations noted.

Hematologic changes indicative of minimal anemia were observed in the 400 mg/kg female group. These changes included a significantly decreased mean red blood cell count relative to the control group, and lower mean values for hemoglobin and hematocrit. In the absence of evidence of increased red blood cell destruction or turnover, these results suggest an interference with erythropoiesis rather than a direct effect on circulating red blood cells.

Male and female rats from the 400 mg/kg dose group had significant increases in mean serum creatinine levels relative to their respective control groups, although the differences were not clearly of biological significance as urea nitrogen levels were not similarly increased. Microscopic examination of the kidneys of the 400 mg/kg animals revealed scattered areas of degeneration of the proximal convoluted tubules in 2 out of 5 animals of each sex. While mean relative kidney weights of all male treatment groups were statistically significantly heavier than their control group, the differences did not fit a dose-related pattern.

Abstract (Cont.)

Male rats from the 400 mg/kg dose group had significantly higher mean serum aspartate transaminase (AST) and sorbitol dehydrogenase (SDH) levels when compared to their control group. While the high-dose female group did not exhibit similar increases, one of the high-dose females did have an elevated SDH level and the mean relative liver weight for the female high-dose group was statistically significantly increased at the 400 mg/kg dose level. Microscopic examination of the livers from the 400 mg/kg animals of both sexes revealed increased severity and wider distribution of chronic focal inflammation in three males and two females when they were compared to their control groups.

In summary, administration of 400 mg/kg/day of the test article for four weeks was associated with erythropoietic, kidney, and liver effects. None of the effects were indicative of more than minor toxicity, and all were most likely reversible. The no-observed-effect level for this subacute toxicity study was 100 mg/kg/day.

FOUR-WEEK ORAL TOXICITY STUDY OF 4-METHYLCYCLOHEXANE METHANOL IN THE RAT

PURPOSE

The purpose of this study was to evaluate the subacute effects of 4-methylcyclohexane methanol when given to rats orally for four weeks.

TESTING FACILITY

Toxicological Sciences Laboratory
Health and Environment Laboratories (HAEL)
B-320 Kodak Park
Eastman Kodak Company
Rochester, NY 14652-3615

TEST ARTICLE CHARACTERIZATION

Chemical Name: 4-methylcyclohexane methanol
HAEL No.: 89-0081
EK Acc. No.: 907670
CAS No.: 34885-03-5
SRID OR Lot No.: X20511-3-3
Experiment No.: 890081G1

PURITY, STABILITY, and CONCENTRATION ANALYSES

The purity of the test article was 97.3% prior to study initiation and 96.6% at study termination, when analyzed by gas chromatography.

Stability of the test article in corn oil was determined by repeated analysis of 1.0 and 20.0% solutions of the test article using gas chromatography on Day 0 and 1, 4, and 9 days after test solution preparation. Concentrations of the test article were 1.0±0%, and 20.0±0% (mean ± SD) prior to storage and 1.0±0%, and 20.0±0% after 9 days of storage, indicating the material was stable in corn oil for at least 9 days.

The concentration of the test article in each batch of test solution was determined prior to use by gas chromatography. The mean concentrations of the test article were 0.6±0.04%, 2.0±0.2%, and 7.8±0.5% (mean ± SD) compared to target concentrations of 0.5, 2.0, and 8.0%.

All analyses were performed by the Chemical Quality Services Division, KP.

TEST PROCEDURE

This study was conducted by methods comparable to OECD GUIDELINES for TESTING of CHEMICALS TG-407, Repeated Dose Oral Toxicity - Rodent: 28-day or 14-day study, and Annex V B.7.

TEST SUBSTANCE EXPOSURE

Rats were given 25, 100, or 400 mg/kg of the test material in corn oil for 21 doses over 29 days. Doses were determined based upon the results of a one week probe study. Doses were given five days per week including holidays. Controls received daily doses of corn oil in volumes equal on a mL/kg body weight basis to those administered to the test groups.

ANIMALS

Five male and five female rats (CD®(SD)BR) from Charles River Laboratories, Kingston, NY, were randomly assigned to each test group. Animals were isolated prior to testing. At the start of the study, rats were approximately 45 (males) or 50 (females) days old and weighed 214±6 g (males) or 173±6 g (females) (mean ± SD). Rats were chosen for this study because they are a common representative species for toxicity studies.

HOUSING

Rats were housed in groups of five segregated by sex. The study was conducted in the vivarium area of Building 320. The study room was maintained at 68-74 °F and 50-61% relative humidity. A photoperiod of 12 hours from 6 a.m. to 6 p.m. was maintained. No other study was housed in the same room as this study. Cages and racks were washed once a week. Absorbent paper under the cages was changed daily.

FEED AND WATER

Agway® Prolab™ Animal Diet (RMH 3200), certified ground chow was fed ad libitum. Feed containers were cleaned weekly. Feed containers were refilled at least once a week. Water was supplied ad libitum through an automatic watering system. The source of the water was the Monroe County Water Authority. No known contaminants in feed or water were expected which would interfere with the outcome of this study.

IDENTIFICATION

All rats were identified by uniquely numbered metal ear tags and ear punches.

RANDOMIZATION

All culling and randomization were done by computer-generated lists using the Automated Animal Toxicology System.

BODY AND FEED WEIGHT DETERMINATIONS

Body weights were collected on Days 0, 4, 7, 14, 21, and 28. Feed consumption was determined on Days 4, 7, 11, 14, 18, 21, 25, and 28.

CLINICAL OBSERVATIONS

Every workday morning each rat was removed from its cage and examined by a trained technician. Immediately after dosing and again in the afternoon, cageside observations were conducted. Cageside observations included, but were not limited to, examination of the hair, skin, eyes, motor activity, feces, and urine. Animals were checked for mortality on weekends.

HEMATOLOGY AND CLINICAL CHEMISTRY EXAMINATIONS

At the time of necropsy, blood was collected from the posterior vena cava while the rats were under CO_2 anesthesia. All assays were conducted by the Animal Clinical Analysis Group, HAEL. Hematology tests included: hemoglobin concentration, hematocrit, red blood cell count, white blood cell count, differential white blood cell count, platelet count, red blood cell indices, and examination of the blood smears for cellular morphology. Clinical chemistry tests included: aspartate aminotransferase, alanine aminotransferase, sorbitol dehydrogenase, alkaline phosphatase, creatinine, urea nitrogen, and glucose.

NECROPSY

Rats were fasted overnight, anesthetized with CO_2, and exsanguinated by severing the posterior vena cava after collecting blood for analysis. Necropsies were conducted according to pathology SOP No. TP 180. The liver, kidneys, adrenal glands, testes, spleen, and thymus were weighed. Paired organs were weighed together. Organ/body weight ratios were calculated. The following organs were fixed in 10% buffered formalin: trachea, lungs, heart, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, pancreas, liver, salivary glands, kidneys, urinary bladder, pituitary gland, adrenal glands, thyroid glands, parathyroid glands, thymus, spleen, mesenteric lymph nodes, bone marrow (femoral), brain, testes, epididymides, male accessory sex glands, ovaries, vagina, uterus, Fallopian tubes, and gross lesions. All tissues were examined microscopically from the control and high-dose groups and gross lesions and target organs were examined from other groups.

STATISTICAL PROCEDURES

Mean values were calculated for body weight, feed consumption, organ weights, hematology, and clinical chemistries. All mean data, except feed consumption, were evaluated using the following computer-generated statistical tests: Bartlett's test ($p \leq 0.01$), one-way analysis of variance (ANOVA) ($p \leq 0.05$), and Duncan's multiple range test ($p \leq 0.05$) to indicate statistical significance. Feed consumption was not analyzed statistically because the animals were group housed.

DATA STORAGE

The final report, tissues, paraffin blocks, slides, data sheets, and all nonperishable raw data were stored in the HAEL archives.

GLP STATEMENT

This study was conducted according to Good Laboratory Practice for Nonclinical Laboratory Studies as promulgated by the Food and Drug Administration, 21 CFR Part 58, December 22, 1978 amended September 4, 1987; Environmental Protection Agency Good Laboratory Practice Standard 40 CFR Part 792, November 29, 1983; and Annex 2 of the OECD Guidelines for Testing of Chemicals (C(81)30 (Final)) as required by Council Directive 87/18/EEC of December 18, 1986.

PROJECT PARTICIPANTS

Study Director	G. J. Hankinson, D.V.M., M.S.
Study Technician	T. S. Hill, A.A.S.
Necropsy Pathologist	M. S. Vlaovic, D.V.M., Ph.D.
Histopathologist	M. S. Vlaovic, D.V.M., Ph.D.
Laboratory Animal Medicine	G. J. Hankinson, D.V.M., M.S.
Hematologist/Clinical Chemist	R. E. Emmons, B.S.
Analytical Chemist	K. A. Robillard, Ph.D.
Report Author	R. S. Hosenfeld, A.A.S.

STUDY DATES

Study Initiation Date	July 14, 1989
Experimental Start Date	July 17, 1989
Experimental Termination Date	November 7, 1989

PROTOCOL AND SOP DEVIATIONS

There were no protocol or standard operating procedure (SOP) deviations.

RESULTS

PROBE STUDY

A probe study was conducted to assist in dose level selection for the four-week study. In the probe study, groups of two male and two female rats were administered 0, 200, 400, or 800 mg/kg/day of the test article in corn oil for a period of five days. Abnormal clinical signs observed in animals receiving doses of 800 mg/kg/day included ataxia and decreased activity in both female rats and decreased activity in one of the two male rats. One of the 800 mg/kg female rats developed signs of severe central nervous system depression. After the fourth dose, this animal became hypothermic and moribund, and was euthanatized. The surviving 800 mg/kg female and one of the 800 mg/kg males lost weight during the study. No abnormal clinical signs were noted for the 400 mg/kg male group. Decreased activity was noted for one of the 400 mg/kg females during afternoon observation periods on Days 2 and 3. This animal appeared normal at all observation times on Day 4. No abnormal clinical signs were seen for the other 400 mg/kg female. No abnormal clinical signs were seen in animals given doses of 200 mg/kg. All animals administered doses of 200 or 400 mg/kg/day gained weight during the study. Based on the results of the probe study, dose levels of 0, 25, 100, and 400 mg/kg/day were chosen for the four-week study.

MORTALITY

No mortality occurred during the four week study.

CLINICAL SIGNS

Sialorrhea following dose administration was seen in the 400 mg/kg male group starting on Day 14 and continuing until study termination. Sialorrhea was found in approximately 50% of the post-dose observations and all five of the high-dose males exhibited this clinical sign at least once in the last two weeks of the study. Discoloration of the hair of face and an unkempt hair coat in the inguinal region were seen in one 400 mg/kg male (Rat #369) on Day 29 of the study. Porphyrin tears were seen on Day 1 in Rat #360, a male from the 25 mg/kg dose group. Both of these observations were not considered treatment-related as they occurred only once and are often seen in control animals. An umbilical hernia was found in one male (Rat #352) from the control group on Day 8. This hernia appeared to have no adverse effect on the animal, and did not affect the outcome of the study.

One 400 mg/kg female (Rat #387) was depressed following administration of the test material on Days 2 and 3. This animal appeared to have had weight loss on Day 4, but subsequently appeared normal. Sialorrhea following dose administration was seen in the 400 mg/kg female group starting on Day 14 and continuing until study termination. Sialorrhea was found in approximately 50% of the post-dose observations and all five of the high-dose females exhibited this clinical sign at least once in the last two weeks of the study. In the 400 mg/kg female group, single rats were observed to have crusts or scaling and alopecia on the face (Rat 389) or alopecia on the back (Rat 386). Such lesions often result from abrasion on cage surfaces or interaction with cagemates and were not considered to be treatment-related.

BODY WEIGHT AND FEED CONSUMPTION

Slightly lower mean body weights were seen during the second week of dosing for all male groups given the test article. The differences in body weight on Day 28 amounted to 1.9%, 4.5%, and 6.1% less than the control mean weight for the low-, mid-, and high-dose groups, respectively. However, these differences were not statistically significant. Body weight growth for the 400 mg/kg female group was retarded between Days 0 and 4, but subsequently recovered, and at termination the mean body weight for this group was just 2.3% less than the control group; this difference was not significant. The low- and mid-dose female groups weighed slightly more than the control group. Mean feed consumption by groups given the test article was not different from the control groups.

HEMATOLOGY

No treatment-related hematology differences were noted for male groups at any dose level. Females from the 400 mg/kg dose group had significantly lower mean red blood cell count, hemoglobin concentration, and hematocrit when compared to the control group. No treatment-related blood cell morphology differences were noted for any dose group. All red blood cell indices were within normal limits indicating the presence of a minimal normochromic, normocytic anemia in the 400 mg/kg female group. Since no evidence of increased red blood cell destruction or turnover was found in other hematology tests, or during necropsy or histopathology examinations, the test article may have had an effect on erythropoiesis, rather than a direct toxic effect on circulating red blood cells.

CLINICAL CHEMISTRY

Both male and female rats from the 400 mg/kg group had significantly higher mean serum creatinine values when compared to their respective control groups. The differences were 16% for males and 13% for females. Mean serum glucose was statistically lower for all male groups treated with the test material when compared to the control value. The apparent decrease in serum glucose values in the treated male rats was due to extremely high serum glucose values in 2 out of the 5 control males. The serum glucose values from treated male rats were not significantly different from historical controls. For the 400 mg/kg male group, there were also significantly higher mean values for serum aspartate aminotransferase (AST) and sorbitol dehydrogenase (SDH) when compared to the control value. The mean AST value for the 400 mg/kg males was 31% higher than the control value. The SDH values for the 400 mg/kg group were variable; individual determinations for four of five animals were higher than those from animals in the other dose levels, and for two animals, they were nearly five-fold higher than the mean value for the control group. There were no statistical differences among female groups for mean glucose, AST or SDH values, although one 400 mg/kg female had an SDH value which was approximately 3.8-fold higher than the mean value for the female control group. No other treatment-related clinical chemistry differences were noted for any dose group of either sex.

ORGAN WEIGHTS

The mean absolute kidney weights for male groups administered the test material were slightly heavier than the mean kidney weight for the control group, though the differences were not dose-dependent. A statistical difference was seen only for the 25 mg/kg group. Relative (to body weight) kidney weights were statistically heavier for all male groups treated with the test material than for the control, but the differences did not follow a dose-related trend. The statistical differences were due to a combination of slightly heavier kidneys and slightly lower mean terminal body weights in all test article-treated male groups. No other differences in organ weights were seen for male rats.

No differences were seen in mean absolute or relative kidney weights for female rats. The mean absolute liver weight was slightly heavier for the 400 mg/kg group than for any other female group, but the difference was not statistically significant. The mean relative liver weight was significantly heavier for the 400 mg/kg female group than for the control group. There were no other significant differences in absolute or relative liver weights or any other differences in organ weights for female groups.

GROSS PATHOLOGY

No treatment-related observations were noted on gross pathology examination for any dose level of either sex.

HISTOPATHOLOGY

In the 400 mg/kg male and female animals, lesions which may be treatment-related included an increased severity of chronic focal inflammation of the liver (3/5 males, 2/5 females), and degeneration of the proximal convoluted tubules of the kidneys (2/5 males, 2/5 females). Similar liver lesions were observed in the control animals, but they were more severe and more widely distributed in the 400 mg/kg dose groups. The kidney lesions for both sexes involved only a few proximal convoluted tubules in each affected animal. No other abnormalities in histology were noted for any dose group of either sex.

DISCUSSION AND INTERPRETATION

In the probe study, doses of 800 mg/kg/day had a narcotic effect on the animals which resulted primarily in transient reduced activity levels and ataxia (females) after dose administration. At this dose level, one of four animals became moribund and was euthanatized. Thus narcosis at 800 mg/kg became a limiting factor in setting dose levels for the subsequent subacute study. Doses of 400 mg/kg/day also resulted in decreased activity in 1 of 2 female rats on the second and third day of dosing. No abnormal clinical signs were noted in the other 400 mg/kg animals or in the 200 mg/kg dose group. Based on the effects observed during the five-day probe study, dose levels of 0, 25, 100, and 400 mg/kg/day were chosen for the four-week study.

Administration of 21 doses of 4-methylcyclohexane methanol in corn oil to rats over a period of four weeks, at dose levels of 25, 100, or 400 mg/kg/day, did not result in mortality.

Sialorrhea following dose administration was noted in both the male and female 400 mg/kg groups from the second week to the end of the study. This condition is not uncommon with gavage studies when a chemical has an odor or a strong smell. One female rat in the 400 mg/kg dose group was depressed for two days during the first week of treatment, but appeared normal thereafter. Other clinical signs were considered incidental to treatment with the test article. Overall, the animals tolerated repeated dosing with the test article well and reduced activity levels which were a prominent clinical effect in the probe study were not prominent in the subacute study.

All male groups given the test material had mean body weights which were slightly lower than the control group. While the weight differences appeared to be dose-dependent, they were not statistically significant and were within the variability levels seen for normal growing rats. Females from the 400 mg/kg group initially lost weight, but recovered within the first week and the other female groups actually weighed slightly more than the control group. This information taken together suggests that the test article may have had a slight effect on the growth of male and female rats at the 400 mg/kg dose level but at lower dose levels, a consistent pattern was not present. Feed consumption was not affected by administration of any of the dose levels.

Hematology tests revealed a decreased mean red blood cell count, and lower hemoglobin and hematocrit levels for the female 400 mg/kg dose group. There were no other hematologic differences noted for any of the other groups. In the absence of any indicators of increased red blood cell destruction or turnover, the presence of a normochromic, normocytic anemia in the 400 mg/kg female group suggests that the test article may have interfered with the erythropoietic process, rather than having a direct effect on circulating red blood cells.

The kidney appeared to be slightly affected by administration of the test material. In the male rats, there were minor but statistically significant higher mean relative kidney weights for all treatment groups, and a significantly higher absolute kidney weight for the low-dose group. Interpretation of these results is difficult because the actual weight differences were small and did not follow a dose-related pattern. The heaviest mean kidney weights, both absolute and relative, were in the low-dose group. The females did not show any significant differences in kidney weights. Mean serum creatinine levels for both males and females at the 400 mg/kg dose level were statistically greater that the control levels. The differences were not clinically significant since the serum urea nitrogen levels were not affected in a similar manner. The highest serum creatinine levels correlated with the kidney lesions observed in the 400 mg/kg male and female rats. If the differences are real, an alternative interpretation of the data is that the test article interfered directly with the clinical chemistry assay for creatinine. Data to address this question directly are not available. Histopathological examination of the kidneys from the 400 mg/kg animals of both sexes revealed the presence of a minimal level of degeneration of the proximal convoluted tubules in 2 of 5 animals of each sex. The pathology data, while not overwhelming, suggest that at the high-dose level the test article had an effect on renal morphology. Functional correlates of the morphologic changes were not readily apparent in spite of the changes in clinical chemistry addressed above.

The liver also appeared to be slightly affected by administration of the test article. Effects on the liver consisted of significant increases in serum aspartate aminotransferase (AST) and sorbitol dehydrogenase (SDH) for the 400 mg/kg male group when compared to the control group. SDH was also higher in one of five female rats at the same dose level. The mean relative liver weight for the 400 mg/kg female group was significantly heavier than for the control group, but absolute liver weights for males and females and relative liver weights in males were not significantly altered by treatment with the test material. Microscopic examination of livers from the 400 mg/kg animals of both sexes revealed chronic focal liver inflammation of minimally increased severity and wider distribution than that seen in the control groups in five (three males, two females) of ten animals. The liver lesions in the 400 mg/kg male rats correlated with the increases in serum SDH but not with the differences in AST levels. The highest SDH levels for the 400 mg/kg females also correlated with the liver lesions.

In summary, administration of the test material for four weeks was associated with relatively minor changes in the erythropoietic system, the kidneys, and the liver at the 400 mg/kg/day dose level. None of the effects were indicative of more than minor toxicity, and all were most likely reversible. The no-observed-effect dose level for this study was 100 mg/kg/day.

TABLES

Tables 1 and 2 summarize the results of this study. Tables, including means and individual data points for body weight, feed consumption, hematology, clinical chemistries, and organ weights, and reports of individual contributors are available as appendices on request.

SIGNATURE PAGE

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REPORT AUTHOR — DATE

Gordon J. Hankinson — April 3, 1990
STUDY DIRECTOR — DATE

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UNIT DIRECTOR, MAMMALIAN TOXICOLOGY SECTION — DATE

John W Hall — April 3, 1990
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M. Susan Jones — 3/28/90
QUALITY ASSURANCE UNIT — DATE

SUMMARY OF REPEATED EXPOSURE STUDY (TABLE 1)

No. rats/group 5, No. of Treatments 21, Days of Experiment 29

Route of exposure: Gavage (mg/kg) Carrier: Corn Oil

Strain: CD®(SD)BR Sex: Male

Exposure concentration:	25	100	400
Weight gain	N*	N*	N*
Feed intake	N	N	N
Daily dose (mg/kg/day)	25	100	400
Clinical signs	*	N	*
Hematology:			
WBC	N	N	N
RBC	N	N	N
Hgb	N	N	N
Hct	N	N	N
MCV	N	N	N
MCH	N	N	N
MCHC	N	N	N
Platelets	N	N	N
Differential	N	N	N

Blood Cell Morphology: No treatment-related abnormalities were observed.

Clinical Chemistry:			
AST (GOT)	N	N	↑ 1
ALT (GPT)	N	N	N
AP	N	N	N
Urea Nitrogen	N	N	N
Glucose	N*	N*	N*
Creatinine	N	N	↑ 1
SDH	N	N	↑ 2
Organ weight:			
Kidneys			
Abs.	N*	N	N
Rel.	↑ 1	↑ 1	↑ 1
Liver			
Abs.	N	N	N
Rel.	N	N	N
Thymus			
Abs.	N	N	N
Rel.	N	N	N
Spleen			
Abs.	N	N	N
Rel.	N	N	N
Adrenal Glands			
Abs.	N	N	N
Rel.	N	N	N
Thyroid Glands			
Abs.	N	N	N
Rel.	N	N	N
Testes			
Abs.	N	N	N
Rel.	N	N	N

Gross pathology: No treatment-related abnormalities were observed.
Histopathology: Treatment-related effects were observed in the liver and kidneys.
Site of toxic action: Liver and Kidneys

Legend

↑ Increased ↓ Decreased 1 Slight 2 Moderate 3 Great N Normal ND Not Done
* See Text

SUMMARY OF REPEATED EXPOSURE STUDY (TABLE 2)

No. rats/group 5, No. of Treatments 21, Days of Experiment 29

Route of exposure: Gavage (mg/kg) Carrier: Corn Oil

Strain: CD®(SD)BR Sex: Female

Exposure concentration:	25	100	400
Weight gain	N	N	N*
Feed intake	N	N	N
Daily dose (mg/kg/day)	25	100	400
Clinical signs	N	N	*
Hematology:			
WBC	N	N	N
RBC	N	N	↓ 1
Hgb.	N	N	↓ 1
Hct.	N	N	↓ 1
MCV	N	N	N
MCH	N	N	N
MCHC	N	N	N
Platelets	N	N	N
Differential	N	N	N

Blood Cell Morphology: No treatment-related abnormalities were observed.

Clinical Chemistry:			
AST (GOT)	N	N	N
ALT (GPT)	N	N	N
AP	N	N	N
Urea Nitrogen	N	N	N
Glucose	N	N	N
Creatinine	N	N	↑ 1
SDH	N	N	N
Organ weight:			
Kidneys			
Abs.	N	N	N
Rel.	N	N	N
Liver			
Abs.	N	N	N
Rel.	N	N	↑ 1
Thymus			
Abs.	N	N	N
Rel.	N	N	N
Spleen			
Abs.	N	N	N
Rel.	N	N	N
Adrenal Glands			
Abs.	N	N	N
Rel.	N	N	N
Thyroid Glands			
Abs.	N	N	N
Rel.	N	N	N

Gross pathology: No treatment-related abnormalities were observed.
Histopathology: Treatment-related effects were observed in the liver and kidneys.
Site of toxic action: Erythropoiesis, Liver, and Kidneys

Legend

↑ Increased ↓ Decreased 1 Slight 2 Moderate 3 Great N Normal ND Not Done
* See Text