Attachment II

Relevant pages from:
"Final Report: 104-Week Dietary Carcinogenicity Study
With 1,2,4-Trichlorobenzene in Mice,
With Cover Letter Dated 6/15/94"
(pages 27 – 30 intentionally omitted)

Attachment II

CODING FORMS FOR SRC INDEXING

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Chemical Category		
1,2,4-TRICHLOROBENZENE		

CMA

CHEMICAL MANUFACTURERS ASSOCIATION

June 15, 1994

VIA MESSENGER

RECD
JUNE 23, 1994
TSCA PICIC

ATTN: TSCA Section 4
Mike Gerel
TSCA Public Information Office
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Room N.E. Mall G102
401 M Street, SW
Washington, D.C. 20460

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TSCA PICIC

RE: Chlorinated Benzenes Final Test Rule: Oncogenicity Testing of 1,2,4-Trichlorobenzene (40 CFR 799.1053); Final Report

Dear Sir/Madam:

The Chemical Manufacturers Association submits six copies of the final report entitled:

"104-Week Dietary Carcinogenicity Study with 1,2,4-Trichlorobenzene in Mice."

The study report is submitted on behalf of the test sponsor, Standard Chlorine Chemical Company, Inc.

Any questions regarding this submission should be directed to the Chlorobenzenes Panel Manager, Dr. Carol R. Stack, at (202) 887-1196.

Sincerely,

Langley A. Spurlock, Ph.D., CAE
Vice President, CHEMSTAR

Enclosures (6)

cc: Michael Stahl, Director, Office of Compliance Monitoring
Roger Nelson, OPPT/CCD/CTIB
Chlorobenzenes Panel, 1,2,4-TCB Task Group

2501 M Street, NW, Washington, DC 20037 Telephone 202-887-1100 Fax 202-887-1237

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WASHINGTON

Sponsor:

Standard Chlorine of Delaware, Inc.
Governor Lee Road
Delaware City, Delaware 19706

FINAL REPORT

Study Title:

104-Week Dietary Carcinogenicity Study with 1,2,4-Trichlorobenzene in Mice

Author:

Michael R. Moore, Ph.D., D.A.B.T.

Study Completion Date:

June 6, 1994

Performing Laboratory:

Hazleton Washington, Inc. (HWA)
1330-B Piccard Drive
Rockville, Maryland 20850

Laboratory Project Identification:

HWA 2603-102

Volume I of IV

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HWA 2603-102

COMPLIANCE STATEMENT
104-Week Dietary Carcinogenicity Study
with 1,2,4-Trichlorobenzene in Mice

This study was conducted in compliance with the Good Laboratory Practice Regulations as set forth in Titl 40 of the U.S. Code of Federal Regulations Part 792, issued November 29, 1983 (effective December 29, 1983), and with any applicable amendments. All deviations from the protocol and/or GLPs are listed in Appendix II. There were no deviations from the aforementioned regulations which affected the quality or integrity of the study or the interpretation of the results in the report.

Study Director:

Michael R. Moore — June 6, 1994

Michael R. Moore, Ph.D., D.A.B.T.
Department of Toxicology

Date

HAZLETON
WASHINGTON

QUALITY ASSURANCE STATEMENT

Study Title: 104-Week Dietary Carcinogenicity Study with 1,2,4-Trichlorobenzene in Mice

Project No.: 2603-102

Quality Assurance inspections and reviews of this study were conducted according to the standard operating procedures of the Quality Assurance Unit and according to the Good Laboratory Practice regulations of the Environmental Protection Agency (EPA - TSCA), Title 40 of the U.S. Code of Federal Regulations Part 792, issued November 29, 1983 (effective December 29, 1983) and with any applicable amendments. These inspections and reviews were performed and findings were reported to the Study Director and management as follows:

Dates of Inspection/Review	Dates Findings Reported to Management/ Study Director	Inspector/Reviewer
Protocol Review:		
2/13/91	2/14/91	S. Ripley
Inspection and/or Data Review:		
3/24-26,28-29,4/5,8/91	4/30/91	B. Munch
6/17,19,24,-25,27-30/91	7/16/91	K. Newland/ B. Munch
9/11-13,16-18,10/1-3,10/91	10/31/91	K. Newland/B. Munch
12/9-11,16,17,31/91;1/2-3/92	1/22/92	B. Munch
3/4,6,9,10,12,13,16,17,19/92	4/7/92	B. Munch
6/5,8,9,11/92	7/14/92	L. Cassell
9/7-9,29/92	10/13/92	D. Hullett
12/7,29/92;1/4/93	1/14/93	S. Ballenger
3/11,22-25,29-31/93	4/16/93	S. Ballenger
Report and Data Review:		
11/4-6,10-12,14-16,18-19,23-24,27-30;12/1-3/93	12/3/93	L. Cassell
1/4-5/94	1/4/94	L. Cassell
6/3,6/94	6/6/94	L. Cassell

Lois Cassell 6/6/94
Lois Cassell Date Released
Quality Assurance Unit

HAZLETON
WASHINGTON

STUDY IDENTIFICATION
104-Week Dietary Carcinogenicity Study
with 1,2,4-Trichlorobenzene in Mice

HWA Study Number:	2603-102
Test Material:	1,2,4-Trichlorobenzene
Study Monitor:	Carol R. Stack, Ph.D. Chemical Manufacturers Association 2501 M Street N.W. Washington, D.C. 20037
Sponsor:	Standard Chlorine of Delaware, Inc. Governor Lee Road Delaware City, Delaware 19706
Study Director:	Michael R. Moore, Ph.D., D.A.B.T. Hazleton Washington, Inc. (HWA) 9200 Leesburg Pike Vienna, Virginia 22182-1699 (703) 893-5400
Study Timetable	
Study Initiation:	December 14, 1990
Initiation of Dosing:	March 13, 1991
Completion of Terminal Necropsy:	March 16, 1993

STUDY PERSONNEL
104-Week Dietary Carcinogenicity Study
with 1,2,4-Trichlorobenzene in Mice

Study Director:	Michael R. Moore, Ph.D., D.A.B.T.
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Clinical Pathologist:	Renée C. Pearson, M.S., D.V.M., Diplomate, American College of Veterinary Pathologists
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Laboratory Supervisor:	Preston L. Burlew, B.A., LATg
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Laboratory Head Technician:	Dalton E. Saunders, LAT

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SUMMARY

1,2,4-Trichlorobenzene was administered daily in the diet to B6C3F1 mice for at least 104 consecutive weeks to evaluate the oncogenic potential of the test material. There were 50 mice per sex in each study group. For Groups 2, 3, and 4, target dietary concentrations of 1,2,4-Trichlorobenzene were 150, 700, and 3200 ppm. The concurrent control (Group 1) was administered the basal diet alone. Parameters evaluated were mortality; clinical observations; body weight, food and compound consumption data; hematology parameters; organ weight data; and necropsy and histopathology findings.

For Groups 2, 3, and 4, during Weeks 1 through 104, the mean daily consumed dose (based on target dietary concentrations) of 1,2,4-Trichlorobenzene was 20.9, 100.5, and 522.0 mg/kg/day, respectively, in the males; and 26.2, 127.2, and 574.9 mg/kg/day, respectively, in the females. The mean daily consumed dose (based on assayed dietary concentrations) was 21.0, 100.6, and 519.9 mg/kg/day, respectively, in the males; and 26.3, 127.0, and 572.6, respectively, in the females of Groups 2, 3, and 4. Therefore, throughout the study, the mean daily dose consumed by females in Groups 2, 3, and 4, was 25.4%, 26.6%, and 10.1% greater, respectively, than the mean daily dose consumed by males in the same dose groups.

The no-observed-effect-level (NOEL) of 1,2,4-Trichlorobenzene for carcinogenicity was 150 ppm; and the no-observed-adverse-effect-level (NOAEL) for systemic toxicity was 150 ppm. A no-observed-effect-level (NOEL) for systemic toxicity was not achieved.

The 3200 ppm dietary concentration produced the following treatment-related effects in males and females: a significant decrease in survival at Week 104; significant depressions of weekly mean body weights and mean total body weight gain; significantly decreased mean food consumption values; increased incidence of urine stains; evidence of a

distended abdomen (in 92% of the males and 80% of the females); liver masses (in 92% of the males and 88% of the females); significantly increased mean liver weight values (absolute and relative to body weight and to brain weight) in the males (no females survived to study termination); hepatocellular carcinomas (in 100% of the males and 92% of the females); hepatocellular adenomas (in 4% of the males and 16% of the females); centrilobular hepatocytomegaly (in 40% of the males and 16% of the females.

The 700 ppm dietary concentration produced the following treatment-related effects in males and females: evidence of a distended abdomen (in 34% of the males and 38% of the females); liver masses (in 74% of the males and 74% of the females); increased mean liver weight values in both sexes (mean absolute and relative to body weight values were significantly increased in the males; mean absolute and relative to body weight and to brain weight values were significantly increased in the females); hepatocellular carcinomas (in 54% of the males and 56% of the females); hepatocellular adenomas (in 32% of the males and 32% of the females); centrilobular hepatocytomegaly (in 54% of the males and 2% of the females.

The 150 ppm dietary concentration also produced the following treatment-related effects: evidence of distended abdomen (in 22% of the males and 26% of the females compared to 12% in the control males and 14% in the control females); increased mean liver weight values (absolute and relative to body weight and to brain weight) in the males and females (all values significantly increased with the exception of the mean liver-to-body weight and liver-to-brain-weight ratios in the males). Although there were gross indications of liver enlargement, microscopically, there was no indication in males or females of increased incidence of hepatocellular carcinomas, adenomas, or centrilobular hepatocytomegaly, compared to the controls.

INTRODUCTION

This study was designed to evaluate the oncogenic potential of 1,2,4-Trichlorobenzene when fed daily to mice for at least 104 weeks. Dosing began on March 13, 1991, and terminal sacrifices were completed on March 16, 1993.

The study was designed in accordance with the US EPA TSCA Health Effects Testing Guidelines, 40 CFR 798.3300 and conducted in compliance with the TSCA Good Laboratory Practices Standards, 40 CFR 792, issued November 29, 1983 (effective December 29, 1983). Protocol and all amendments are presented in Appendix 10; deviations from protocol and/or GLPs are presented in Appendix 11.

TEST AND CONTROL MATERIALS

The test material, 1,2,4-Trichlorobenzene, lot No. 071486, a clear, colorless liquid, was received from the Sponsor on December 19, 1990, and stored at room temperature (protected from light). The purity was reported to be 98.9%. Information on the methods of synthesis and stability, as well as data on composition or other characteristics which define the test material, is on file with the Sponsor.

Purina® Certified Rodent Chow® #5002 was used as the basal and control feed.

A reserve sample of the test material (10 g) was taken prior to initiation and stored at room temperature (protected from light). The sample will be archived at HWA.

Following completion of the in-life phase, the Testing Facility disposed of all remaining test material.

TEST ANIMALS AND HUSBANDRY

A total of 530 (266 males and 264 females) approximately 4-week-old $B_6C_3F_1$/CrlBr VAF/Plus® mice was received on February 26, 1991, from Charles River Laboratories, Inc., Raleigh, North Carolina. Animals were assigned temporary animal numbers, acclimated to laboratory conditions for approximately 2 weeks, and released for study use by a staff veterinarian. During the acclimation period, five animals/sex were randomly selected and examined for the presence of pathogenic endo- and ectoparasites using standard screening procedures and serology assays for common laboratory viruses. There was no evidence of pathogenic endo- or ectoparasites or viruses.

Caging Conditions - Upon receipt, the animals were housed two/cage in suspended stainless-steel, wire-mesh cages. Animal cages and racks were sanitized once every 2 weeks; excreta trays beneath the animal cages were changed at least three times/week.

Feed and Water - Purina® Certified Rodent Chow® #5002 was available ad libitum during the acclimation and study periods, unless otherwise noted. The feed was analyzed by the manufacturer for concentrations of specified heavy metals, aflatoxin, chlorinated hydrocarbons, organophosphates, and specified nutrients. Tap water, via an automatic watering system or water bottle (changed twice weekly), was available ad libitum during the acclimation and study periods. The water is routinely analyzed for environmental contaminants and specific microbes. Results of feed and water analyses are on file at HWA.

The Study Director and/or Sponsor considered the possibility of interfering substances potentially present in animal feed and water, including the test material itself or possible structurally related materials. None of these contaminants were reasonably expected to be present in animal feed or water at levels sufficient to interfere with this study.

Environmental Conditions - Controls were set to maintain the temperature at 72 ± 6°F with a relative humidity of 50 ± 20%. Ten or greater air changes/hour were maintained in each housing room and a 12-hour light/12-hour dark cycle were maintained. Animal racks were rotated around the animal room every 2 weeks.

Justification of Species - The mouse was selected for use on this study because mice historically have been used in safety evaluation studies and are recommended by the appropriate regulatory agencies.

METHODS

Group Assignment and Dosage Levels

Animals were initially accepted into the randomization pool based upon physical examinations; animals with findings were eliminated from the randomization pool. A total of 400 mice (200/sex) was assigned to study using a computerized weight randomization program by first eliminating the animals with extreme body weights and then selecting the random assignment which produced homogeneity of variance and means by Bartlett's test (1937) and one-way analysis of variance (ANOVA). At the time of randomization, the weight variation of the animals selected did not exceed ±20% of the mean body weight for each sex, and the mean body weight for each g oup of each sex was not statistically different. Animals were assigned to groups as follows:

Group	Dietary Level[a] ppm	Number of Animals Male	Number of Animals Female	Animal Numbers Male	Animal Numbers Female
1 (Control)	0	50	50	A5249-A5298	A5299-A5348
2 (Low)	150	50	50	A5349-A5398	A5399-A5448
3 (Mid)	700	50	50	A5449-A5498	A5499-A5548
4 (High)	3200	50	50	A5549-A5598	A5599-A5648

[a] Based on the compound volatility the diets were prepared 10% higher than target

During the randomization process, the study animals were assigned unique individual numbers and individually housed. The animals were permanently identified by a BioMedic® microchip identification device implanted subcutaneously. Due to the volatility of the compound, each group was housed in a separate room to minimize possible contamination.

At initiation of dosing, the animals were approximately 6 weeks of age with body weights ranging from 19 to 26 g for the males and 16 to 22 g for the females.

Animals not used on study were removed from the study rooms and euthanized.

Compound Formulation and Administration

The test material was assumed to be 100% for dosage calculation purposes. For each dietary level, the test material and basal feed were weighed on an appropriate balance (mg or kg) into a glass beaker or weigh pan, respectively. Approximately 200 g of compacted feed was transferred into a Waring blender. The weighed amount of test material in the glass beaker was then transferred into a Waring blender by rinsing the beaker with feed taken from the weigh pan, and adding the feed rinses to the blender. The resulting premix was then blended for approximately 2 minutes to ensure an apparent homogeneous mixture. The premix was transferred to a Patterson-Kelley twin-shell mixer (fitted with an intensifier bar) containing the remaining required amount of basal feed. The dietary formulation was then mixed for 1 minute/kg.

Fresh diets were prepared weekly at 110% of actual target concentration and frozen prior to use. The test diets were available to the animals 7 days/week (unless otherwise noted) for at [illegible] 104 weeks and were available until the day prior to necropsy. The control [illegible] were fed Purina® Certified Rodent Chow® #5002 in the same manner as the test animals.

Reserve samples of each weekly formulation were taken and stored in the freezer. The reserve samples will be discarded after the issuance of the final report.

The test material was administered via the diet because the potential human exposure is by the oral route.

Analysis of Prepared Formulations

Bulk Chemical Analysis - The bulk chemical purity of 1,2,4-Trichlorobenzene was determined prior to treatment, approximately every 6-months, and at termination.

Homogeneity - For this study and the companion rat study (HWA No. 2603-103), evaluation for homogeneity was performed on representative formulations for the low-dose (100 ppm) for the rat study and the high-dose (3200 ppm) for the mouse study. The same formulation batch size (36 kg) and mixing procedure were used for both studies.

Stability - For the low- and high-dose formulations (100 ppm and 3200 ppm, respectively), analyses were conducted prior to initiation of dosing to assess the stability of analytical samples stored frozen in glass jars for 0, 7, and 21 days; and for aliquots of the test diets stored frozen in glass jars (same manner of storage used for diets presented to the animals) for 0 and 10 days. For the analytical samples, additional analyses were conducted to assess Day 58 freezer stability from formulations prepared for Week 80 (HWA 2603-102) and Day 62 freezer stability from formulations prepared for Week 76 (HWA 2603-103). Analyses were performed in duplicate from samples stored in the freezer.

Concentration Analyses - Samples of each male and female formulation taken from animal feeders at Weeks 1, 2, 3, 4 and every 4 weeks thereafter were analyzed in duplicate for concentration of the test material. Feed was analyzed for initial concentration and after a 2- and 3-day presentation to the animals. For each study group, the male and female composite ending diet samples were prepared by dumping the contents

from either 2 male or 2 female feeders (as approximate) into a glass jar (approximately 1 gallon), capping the jar and gently mixing the contents. The contents were then transferred to a clean glass sampling jar, filled to leave no head space and immediately capped with Teflon®-lined lids. For the Group 1 ending diet sample, the residual feed from 2 male and 2 female feeders was combined as a single sample for assay.

Analytical Method - The analytical method used to assay the level of test article in the diet involved extraction of the test article from the feed mixture using iso-octane and analysis using gas chromatography and an electron capture detector (ECD). The method is fully outlined in Appendix 1.

Observations and Records

Mortality and Clinical Observations - The mice were observed for mortality and moribundity twice daily. A thorough physical examination was conducted weekly. A careful cageside observation for obvious indications of toxic effects was performed once daily.

Body Weight and Food Consumption - Body weights were measured and recorded at randomization, prior to treatment, weekly for 16 weeks, and every fourth week thereafter and at Week 105. Food consumption was measured and recorded weekly for Weeks 1-16 and every fourth week thereafter. When obvious spillage or wastage of food was recorded during the detailed physical examination, the estimate of food consumption for that animal was excluded from the calculation of group mean food consumption during the affected interval.

Clinical Pathology

During Weeks 52 and 78 of treatment all animals were sampled for hematology via tail clip. Animals were bled in ascending order and were alternated between sexes. At termination all surviving animals were fasted overnight with water available prior to clinical hematology

sampling via tail clip. At termination the sampling sequence was the same as the necropsy sequence. Each group was sampled (independently of the other study groups) during the same phase of the diurnal cycle. The blood smears were used to determine cellular morphology and leukocyte differentials for the Group 1 and 4 animals for all intervals and the Group 3 animals for Weeks 52 and 105. Samples were also taken on moribund animals prior to sacrifice when possible.

Terminal Studies

Sacrifice and Gross Pathology - All animals which were found dead or sacrificed in extremis during the study were subjected to a gross postmortem examination. All surviving animals were fasted overnight, weighed the day of scheduled necropsy, given an intraperitoneal injection of sodium pentobarbital, and exsanguinated. Necropsies were performed on all animals by appropriately trained personnel using procedures approved by board-certified pathologists. Each scheduled necropsy was performed under the direct supervision of a veterinary pathologist. Necropsies included examination of the following:

all orifices
carcass
cervical tissues and organs
cranial cavity
cut surfaces of the brain (if processed)
external surface of the body
external surface of the brain
external and cut surfaces of the spinal cord (if processed)
nasal cavity and paranasal sinuses
thoracic, abdominal, and pelvic cavities and their viscera

All findings were recorded.

Organ Weights - At terminal sacrifice the following organs from the first 10 mice/sex/group were weighed (the liver with gallbladder was also weighed from all animals that were sacrificed on the third and fourth day of the terminal sacrifice) after careful dissection and trimming of fat and other contiguous tissue:

brain with brainstem
kidneys
liver with gallbladder
testes with epididymides

Organ-to-terminal-body-weight ratios were calculated using the fasted terminal body weight recorded at necropsy. Organ-to-brain-weight ratios were also calculated.

Tissue Preservation - The following tissues (when present) from each animal were preserved in 10% neutral-buffered formalin:

adrenals
brain with brainstem (medulla/pons, cerebellar cortex, and cerebral cortex)
cervical spinal cord
colon, cecum, rectum
duodenum, jejunum, ileum
esophagus
eyes
femur with bone marrow
heart
kidneys
lesions
liver with gallbladder
lumbar spinal cord
lung
mammary gland (females only)
mandibular lymph node
masses and associated tissues
mesenteric lymph node
mid-thoracic spinal cord
ovaries
pancreas
pituitary
prostate
salivary glands (mandibular)
sciatic nerve
seminal vesicles
skeletal muscle
skin
spleen
stomach
testes with epididymides
thymus
thyroid/parathyroids
trachea
urinary bladder
uterus with vagina and cervix

Histopathology - Preserved tissues from all scheduled sacrifice animals in Groups 1 and 4, and all animals from all groups which were found dead or sacrificed in extremis, were embedded in paraffin, sectioned, stained with hematoxylin and eosin, and examined microscopically. Gross lesions were also examined from all animals in Groups 2 and 3. As potential target organs, the liver with gallbladder, adrenal (cortex and medulla), testes and seminal vesicles from all animals

in Groups 2 and 3 were embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Subsequent microscopic examination included the livers from all Group 2 and 3 terminal-sacrifice animals; and the adrenal (cortex and medulla), testes, and seminal vesicles from the Group 3 animals.

Statistical Analyses

Cumulative survival data (All Groups and Groups 1, 2 and 3) were analyzed using the National Cancer Institute Package. Trend analysis of survival was evaluated at the 5.0% one-tailed probability level.

Weekly body weights, body weight change (Weeks 1-14, 14-24, 24-52 52-104, 1-80, and 1-104), weekly food consumption, total food consumption (Weeks 1-4, 5-8, 9-13, 14-24, 24-52, and 52-104), clinical pathology data (excluding cell morphology gradings), terminal body weights, and organ weight data of the control group were compared statistically to the data from the same sex of the treated groups. Statistical analyses were performed as diagrammed in Figure 1.

If variances of untransformed data were heterogeneous, a series of transformations was performed in an effort to achieve variance homogeneity. When the series of transformations was not successful in achieving variance homogeneity, analyses were performed on rank-transformed data. Group comparisons were routinely performed at the 5% two-tailed probability level.

Statistical significance is designated throughout the text of this report by the term *significant*. Data transformations are presented in Appendix 9.

Specimen, Raw Data, and Final Report Storage

All tissue specimens, blocks and slides, raw data, and the final report will be retained by Hazleton Washington, Inc., in accordance with GLP requirements.

RESULTS

Analytical Chemistry

Results of pretest analyses for homogeneity, stability, and routine concentration are presented in Table 1.

Homogeneity analyses (low- and high-dose levels) indicated that the test material was homogeneously mixed; relative standard deviation (RSD) values were within 5%. Stability analyses of the 100 and 3200 ppm dose levels indicated that frozen aliquots of the formulations (for subsequent presentation to the animals) were stable for up to 10 days; and frozen analytical samples of the formulations were stable for up to 58 days (100 ppm) and 62 days (3200 ppm). All values were within ±10% of initial concentration.

Results of routine concentration analyses indicated that all initial formulations were within ±11% of actual target concentrations. The test material has been previously shown to evaporate at approximately 5% per day from test diets. At most of the sampling intervals the majority of loss in concentration occurred between Days 1 and 2 with the greatest loss in the low-dose formulation. Results of the 2-day analysis indicated a loss of approximately 20-30% from the initial concentration; a smaller loss was seen from Days 2 to 3.

In-life Observations

Mortality - Cumulative adjusted survival through Week 104 is presented in Table 2 and depicted graphically in Figure 2; individual animal disposition is presented in Appendix 2.

Survival rates on the first day of Week 105 were 90, 88, 82, and 10% for the Group 1-4 males and 78, 76, 84, and 0% for the Group 1-4 females, respectively. Statistical evaluation of survival data revealed a significant decrease in the survival of the high-dose males and females. Additionally, a significant negative trend was seen for the males and

females; this significance is attributed to the mortality in the high-dose animals. Survival rate statistics were also conducted on Groups 1, 2, and 3 only. There were no significant differences in the survival of either the males or females when Group 4 was excluded.

Clinical Observations - A summary of daily cageside and weekly physical observations is presented in Table 3. Individual observations are presented in Appendix 3.

The majority of abnormalities noted during cageside and physical examinations have been incidental findings, unrelated to test material administration. A treatment-related clinical abnormality is "distended abdomen" for which the incidence in the high-dose males and females (Group 4) is a direct correlation to enlarged livers and liver masses observed in unscheduled deaths from Group 4. Convulsions observed primarily in the low- and mid-dose males, are not related to trichlorobenzene administration. After being handled, an extensor-thrust spasm often occurs in B6C3F1 mice, and this spasm (as noted in the raw data) is being noted as "convulsion". There has been no evidence of "spontaneous convulsion" (without prior handling) in any of the groups.

Additionally, palpable tissue masses (small < 1 cm (d) ≤ large) have been detected in both sexes. However, such masses are primarily external, for which the current incidence of most was not treatment-related.

Body Weights - Mean body weight data are presented in Table 4A and depicted graphically in Figure 3; total body weight change data (Weeks 1-14, 14-24, 24-52 52-104, 1-80, and 1-104) are presented in Table 4B. Individual body weight and body weight change data are presented in Appendices 4A and 4B, respectively.

Statistically significant values in mean body weight and body weight change data are summarized in Text Tables 1 and 2, respectively.

Figure 2
Adjusted Percent Survival

Group 1 Group 2 Group 3 Group 4

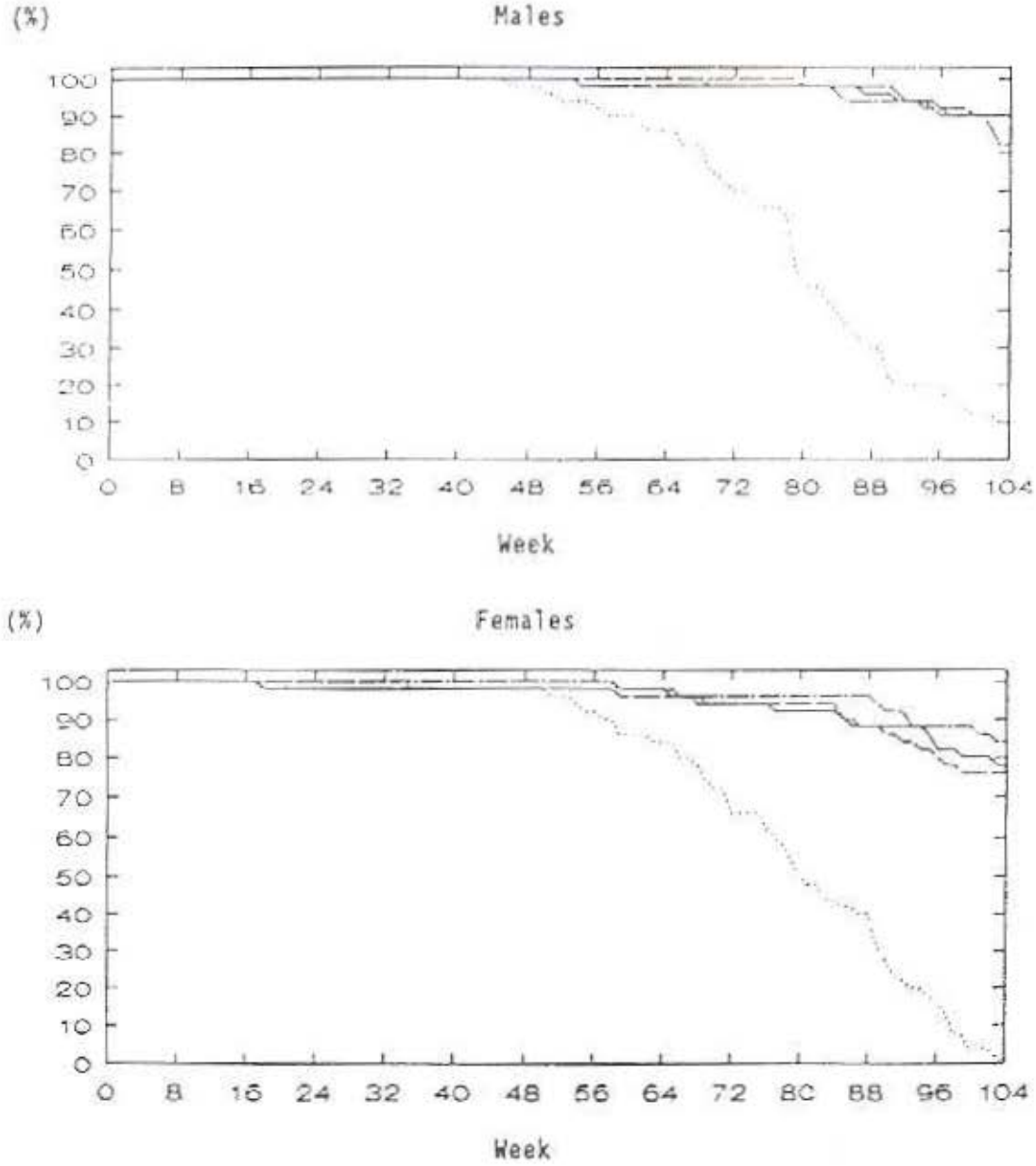

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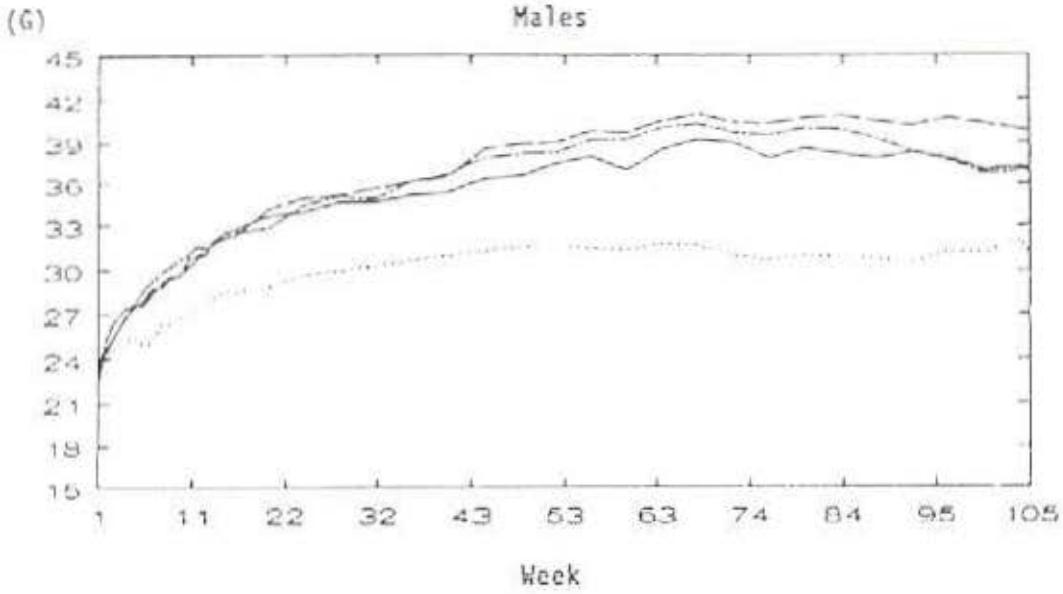
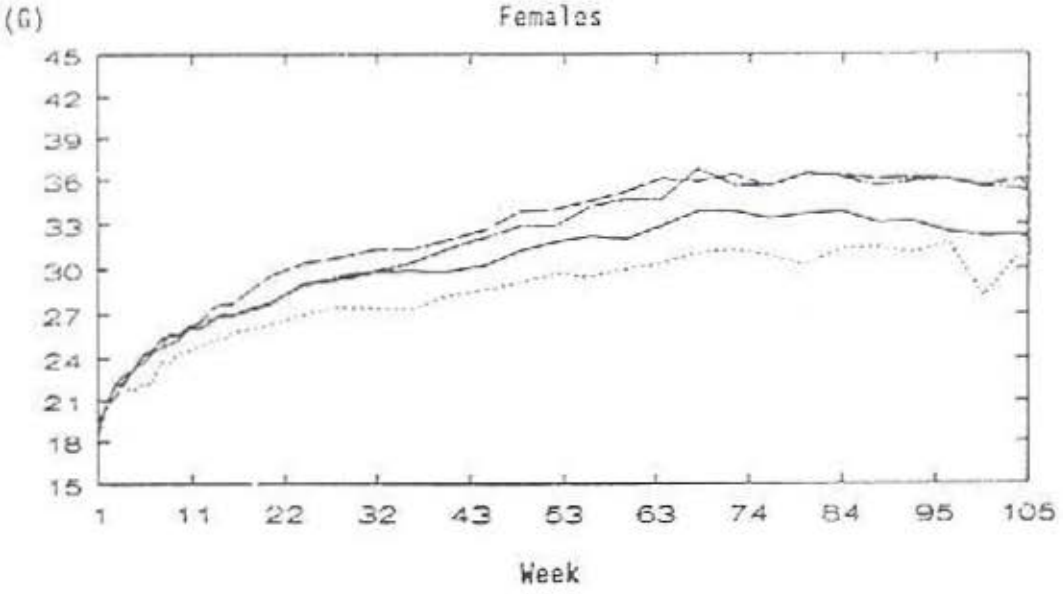
Figure 3
Mean Body Weights

Group 1 Group 2 Group 3 Group 4





Text Table 2
Statistically Significant Findings
Body Change Weight Data

Parameter	Group:	Males 2	Males 3	Males 4	Females 2	Females 3	Females 4
WEEKS 1-14				↓	↑	↑	
WEEKS 14-24		↑					↓
WEEKS 24-52				↓	↑	↑	
WEEKS 1-80				↓	↑	↑	↓
WEEKS 1-104		↑		↓	↑	↑	

Key: ↓ = Significantly decreased, $p \leq 0.05$.
↑ = Significantly increased, $p \leq 0.05$.

Compared to control mean values, significantly lower weekly mean body weights were noted only in the Group 4 (3200 ppm) males and females except for the Group 2 females at Weeks 1, 3, 4, and 6. Conversely, weekly mean body weights were greater (frequently statistically significant) in the Group 2 and 3 animals compared to control. Mean body weight change was lower (statistically significant) only in the Group 4 animals (Weeks 1-14, 24-52 and 1-104 for the males and Weeks 14-24 and 1-80 for the females). Conversely, body weight change in both sexes of Group 2 (Weeks 14-24 and 1-104 for the males and Weeks 1-14, 24-52, 1-80 and 1-104 for the females), as well as the Group 3 females (Weeks 1-14, 24-52, 1-80 and 1-104), was significantly greater compared to the controls.

Food Consumption - Mean food consumption data are presented in Table 5A and depicted graphically in Figure 4; mean total food consumption data (Weeks 1-4, 5-8, 9-13, 14-24, 24-52, and 52-104) are presented in Table 5B. Individual data are presented in Appendix 5.

Statistically significant values in mean weekly and total food consumption data are summarized in Text Tables 3 and 4, respectively.

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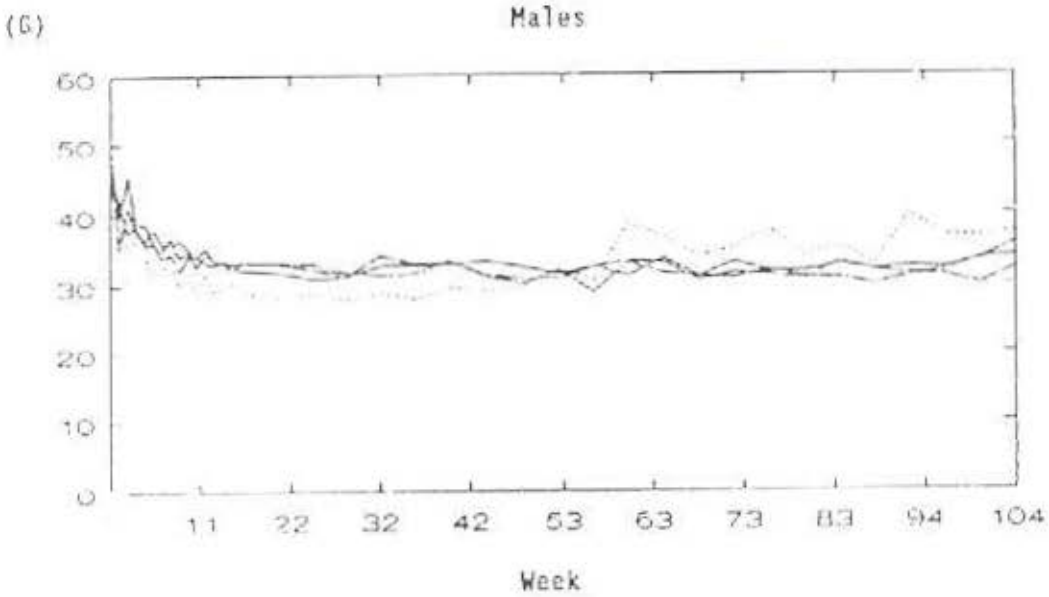
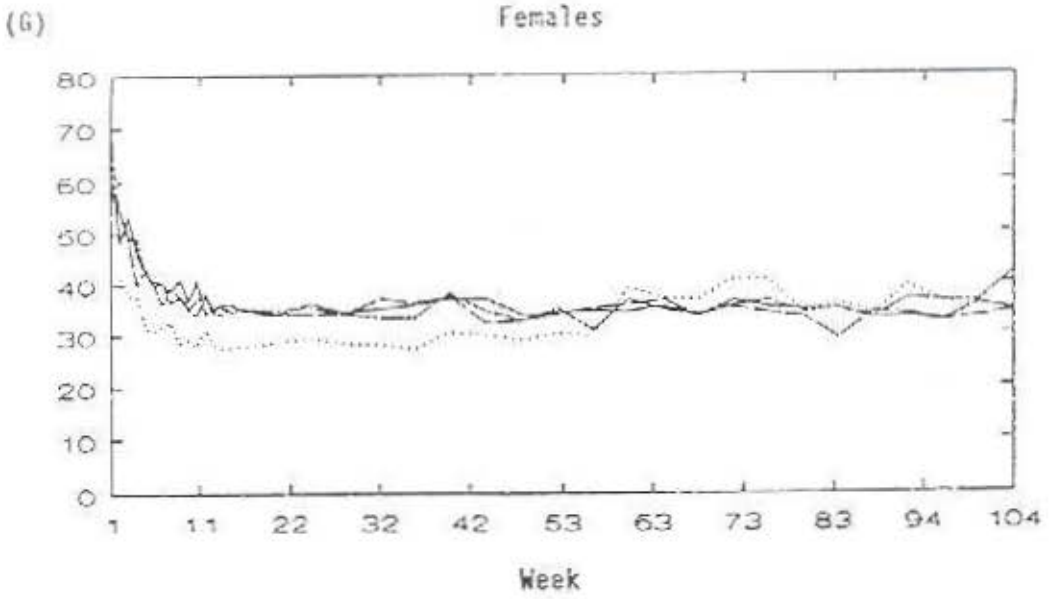
Figure 4
Mean Food Consumption

Group 1 Group 2 Group 3 Group 4





Clinical Pathology

Mean hematology values are presented in Table 7 and individual data are presented in Appendix 7A and 7B for Weeks 52, 78 and 105 and moribund animals, respectively. Findings are further discussed in the Clinical Pathology Report.

Hematology - The mean values for percentage segmented neutrophils were significantly increased in Group 3 animals but decreased in Group 4 animals at Week 52 and significantly increased in Group 4 males at Week 105. Mean percentage lymphocyte values were significantly decreased in Group 3 animals and increased in Group 4 animals at Week 52 and significantly decreased in Group 4 males at Week 105. Significant decreases were observed in the mean values for percentage monocytes in Group 4 females at Week 52 and eosinophils in Group 4 males at Week 52, Group 4 animals at Week 78, and Group 3 females at Week 105. The aforementioned changes are considered to be incidental to the administration of the test material.

There was no evidence of an effect of the test material on the relative differential leukocyte counts or cellular morphology for moribund-sacrifice animals.

Terminal Studies

Gross Pathology - Gross pathology findings are summarized in Tables 8A, 8B and 8C for unscheduled deaths, terminal sacrifices, and all animals, respectively. Individual gross pathology findings are presented in Appendix 8.

There was a higher incidence of liver masses, enlarged livers, irregularly-shaped livers and pale kidneys observed for the Group 4 males and females among the unscheduled deaths. Other findings were sporadic and not related to treatment.

Treatment-related findings observed at the terminal sacrifice were limited to an increased incidence of liver masses in the Group 3 and 4 males and the Group 3 females. Other observations were sporadic and not related to treatment.

Organ Weights - Mean fasted terminal body weights, absolute organ weights, organ-to-terminal-body-weight, and organ-to-brain-weight ratios are presented in Table 9. Individual data are presented in Appendix 8.

Evaluation of the terminal body weight data revealed statistically increased values for Group 2 animals and for the Group 3 females; and decreased values for the Group 4 males when compared to control values. Evaluation of the organ weight data revealed statistically increased absolute liver values for the Group 2 and 3 animals and the Group 4 males: increased liver-to-body weight ratio for the Group 2 females, Group 3 animals and the Group 4 males; increased liver-to-brain weight ratio for the Group 2 and 3 females and the Group 4 males; decreased brain-to-body weight ratio for the Group 2 males; increased absolute testes with epididymides weights and testes with epididymides-to-brain weight ratio for the Group 2 males; and decreased absolute testes with epididymides weights; testes with epididymides-to-body weight ratio and testes with epididymides-to-brain weight ratio for the Group 4 males.

Histopathology - Microscopic findings are summarized in Tables 10A, 10B, and 10C for unscheduled deaths, terminal sacrifices, and all animals, respectively. Individual histopathology findings are presented in Appendix 8. The findings are further discussed in the Pathology Report.

Microscopic evaluation of the liver revealed an increased incidence of hepatocellular carcinoma in the Group 3 and 4 males and females (100% of examined Group 4 males, 92% of Group 4 females, 54% of Group 3 males, and 56% of Group 3 females). Adenomas were also increased

in incidence in the same groups (except for Group 4 males, in which they were likely overwhelmed by the extent of carcinoma development). Also present within liver tissue, and clearly associated directly with 1,2,4-Trichlorobenzene exposure, was enlargement of hepatocytes within the centrilobular zone of livers from many males of Groups 3 and 4.

Findings with increased incidences not related to treatment with 1,2,4-Trichlorobenzene included increased congestion/hemorrhage of the corticomedullary junction of the adrenal cortex of the Group 4 males and females; decreased secretion of the seminal vesicles of the Group 4 males; and increased congestion/hemorrhage in the lungs of the Group 4 males and females.

All other histologic changes were comparably distributed between examined groups and of the type and general frequency usually encountered in normal populations of mice of this strain and age.

DISCUSSION AND CONCLUSION

1,2,4-Trichlorobenzene was administered daily in the diet to B6C3F1 mice for at least 104 consecutive weeks. There were 50 mice per sex in each study group. For Groups 2, 3, and 4, target dietary concentrations of 1,2,4-Trichlorobenzene were 150, 700, and 3200 ppm. Mice in Group 1 were administered the basal diet alone and served as the concurrent control group. Due to volatility of the test material, each study group was housed in a separate room to prevent any cross-contamination of test material between dose groups.

Dietary administration of 1,2,4-Trichlorobenzene was required by the EPA test rule (40 CFR Part 799.1053; Federal Register Vol. 51, pp. 24657-24667, July 8, 1986). Due to the volatility of the test material, precautions were taken to maximize the dietary intake of 1,2,4-Trichlorobenzene by the test animals at the prescribed dietary concentrations. The dietary formulations of 1,2,4-Trichlorobenzene for Groups 2, 3, and 4, were prepared weekly at 110% of target concentration. The dietary formulation of 1,2,4-Trichlorobenzene for each study group (as well as basal diet for Group 1) was then aliquoted into labeled glass jars (each approximately 1-gallon volume, and sealed with a Teflon-lined lid) and stored frozen until needed for presentation to the animals. Three times during each study week, the residual diet in each animal's feeder was replaced with fresh diet (removed from frozen storage). Therefore, dietary formulations of 1,2,4-Trichlorobenzene remained in the animal's feeders for a maximum of 3 days before being replaced with fresh diet containing the appropriate concentration of 1,2,4-Trichlorobenzene.

Periodically throughout the study, the dietary formulations of 1,2,4-Trichlorobenzene were sampled at the time of preparation and found to be >100% of target concentration (except for the Week 2, low-dose formulation, and the Week 72 low- and mid-dose formulations, where the dietary concentrations of 1,2,4-Trichlorobenzene were $\geq$ 95.7% of target

concentration). Analyses also indicated that dietary formulations of 1,2,4-Trichlorobenzene were stable for up to 10 days under the conditions maintained for frozen storage of aliquots subsequently presented to the animals. Also periodically throughout the study, samples of the residual 1,2,4-Trichlorobenzene dietary formulations remaining in the animal's feeders after either a 2-day or 3-day feeding interval were collected and analyzed. Results indicated that dietary concentrations of 1,2,4-Trichlorobenzene decreased at an average rate of approximately 10% per day. Throughout the study, the lowest mean concentration of 1,2,4-Trichlorobenzene detected in a residual feed sample was 62.7% of target concentration after a 3-day feeding interval (Group 2 at Week 1).

For Groups 2, 3, and 4, during Weeks 1 through 104, the mean daily consumed dose (based on target dietary concentrations) of 1,2,4-Trichlorobenzene was 20.9, 100.5, and 522.0 mg/kg/day, respectively, in the males; and 26.2, 127.2, and 574.9 mg/kg/day, respectively, in the females. The mean daily consumed dose (based on assayed dietary concentrations) was 21.0, 100.6, and 519.9 mg/kg/day, respectively, in the males; and 26.3, 127.0, and 572.6, respectively, in the females of Groups 2, 3, and 4. Therefore, throughout the study, the mean daily dose consumed by females in Groups 2, 3, and 4, was 25.4%, 26.6%, and 10.1% greater, respectively, than the mean daily dose consumed by males in the same dose groups.

The high-dose of 1,2,4-Trichlorobenzene produced a significant decrease in survival. At Week 104, survival rates in Groups 1, 2, 3, and 4, were 90, 88, 82, and 10%, respectively, in the males; and 78, 76, 84, and 0%, respectively, in the females. The treatment-related decrease in survival in Group 4 occurred during the second year of the study; however, at least 58% of the high-dose males and females survived through 78 consecutive weeks of 1,2,4-Trichlorobenzene administration. In Groups 1, 2, 3, and 4, survival rates on the first day of Week 52 were 100, 100, 100, and 96%, respectively, in the males; and 98, 98, 100, 96%,

respectively, in the females; and at Week 78, survival rates were 98, 98, 98, and 64%, respectively, in the males; and 92, 94, 96, and 58%, respectively, in the females.

Treatment-related abnormalities were also noted during daily cageside and weekly physical examinations. Reflecting the increased incidence of mortality in Group 4, the incidence for typical indications of ante-mortem condition (hunched posture, hypoactive, dyspnea) were also notably increased in Group 4. A dose-related increase for distended abdomen was indicative of the dose-related induction of liver enlargement and liver neoplasms with associated accumulation of ascitic fluid. In Groups 1, 2, 3, and 4, the incidence of animals exhibiting distended abdomen was 12, 22, 34, and 92%, respectively, in the males; and 14, 26, 38, and 80%, respectively, in the females. An increased incidence of urine stains in the high-dose (Group 4) males and females (30 and 28%, respectively, compared to 8 and 6% in the control males and females, respectively) was also a treatment-related finding of undetermined etiology. All other clinical abnormalities were incidental findings, unrelated to 1,2,4-Trichlorobenzene administration, including the notation of "convulsion". "Convulsion" was noted during animal observations to describe the extensor-thrust spasm that often occurs in B6C3F1 mice after they have been handled. As documented in the raw data for the current study, spasms or convulsions only occurred immediately after the mice had been handled, and were not observed at any other time.

A treatment-related depression of body weight gain occurred only in the high-dose (Group 4). Throughout the study, with few exceptions, weekly mean body weights for the Group 4 males and females were significantly lower compared to the control mean values. Accordingly, mean total body weight gain was significantly lower during Weeks 1 through 80 in the Group 4 males and females, and was significantly lower during Weeks 1 through 104 in the Group 4 males (no Group 4 females survived to Week 104). For males and females in the low- and mid-dose (Groups 2 and 3),

weekly mean body weight values, as well as mean total body weight gain values were generally equal to or greater than control group mean values.

Especially during Weeks 1 through 12, food spillage/waste by mice in all groups, including the controls, negated the measurement of food consumption for those mice with spilled feed. However, the incidence of feed spillage/waste was notably decreased in the high-dose (Group 4) mice compared to the other groups, and was likely an indication of food avoidance due to poor palatability of the 1,2,4-Trichlorobenzene/diet mixture. After modifications of the feeder failed to substantially decrease the incidence of spilled feed, a different type of feeder was used for the remainder of the study (beginning with Week 15). During the first 16 weeks, and continuing throughout the study, weekly mean food consumption values in the Group 4 males and females were notably lower, frequently significantly lower, compared to the control mean values. Conversely, beginning in Week 2 and continuing throughout the study, weekly mean food consumption values in the Group 3 males and females were generally equal to or greater than control mean values. Although poor palatability may have been a contributing factor to the decreased food consumption by the Group 4 mice, systemic toxicity in the Group 4 mice was evident from clinical abnormalities and necropsy findings in unscheduled deaths. Therefore, the decreased food consumption in Group 4 was considered a treatment-related effect.

Evaluation of hematology parameters, including cell morphology, during Weeks 52, 79, and 105, indicated no toxic or carcinogenic effect on the hematopoietic system due to dietary administration of 1,2,4-Trichlorobenzene at any dose level, including the high-dose (3200 ppm). However, necropsy and histopathology findings clearly indicated the liver in mice to be a target organ for 1,2,4-Trichlorobenzene, resulting in the induction of hepatic toxicity and carcinogenicity.

The liver was examined microscopically from all animals in all study groups (with the exception of one control male for which hepatic

autolysis precluded definitive histopathologic examination). In Groups 1, 2, 3, and 4, the incidence of hepatocellular carcinoma was 8/49, 5/50, 27/50, and 50/50, respectively, in the males; and 1/50, 1/50, 28/50, and 46/50, respectively, in the females. For hepatocellular adenoma, the incidence in Groups 1, 2, 3, and 4, was 4/49, 7/50, 16/50, and 2/50, respectively, in the males; and 3/50, 4/50, 16/50, and 8/50, respectively, in the females. In addition to the induction of hepatic adenomas and carcinomas in the mid- and high-dose mice, 1,2,4-Trichlorobenzene administration caused centrilobular hepatocytomegaly in Group 3 and 4 mice with and without concurrent hepatic neoplasia. In Groups 1, 2, 3, and 4, the incidence of centrilobular hepatocytomegaly was 0/49, 0/50, 27/50 and 20/50, respectively, in the males; and 0/50, 0/50, 1/50, and 8/50, respectively, in the females.

Necropsy findings for the liver were predictive of the increased incidence of neoplasia in the mid- and high-dose groups. In Groups 1, 2, 3, and 4, the percent of mice exhibiting liver masses was 24, 22, 74, and 92%, respectively, in the males; and 10, 16, 74, and 88%, respectively, in the females. The incidence for mice exhibiting abdominal ascitic fluid, as well as visibly enlarged or irregularly shaped livers were notably increased only in the high-dose group compared to the controls.

Although the incidence for liver neoplasia and masses were not increased in the low-dose (Group 2) mice compared to the controls, organ weight data indicated a dose-related increase for liver weight in males and females. Compared to control mean liver weight values, the absolute and relative (to body weight) mean values for liver weight were significantly increased, with a dose-related pattern, in all 1,2,4-Trichlorobenzene dose groups (except for the Group 4 females, none of which survived to study termination). A dose-related increase was also evident for the mean liver-to-brain weight ratio, but the mean values were significantly greater only in the Group 4 males, and Group 2 and 3 females

Except for the liver, all other tissues examined histopathologically from the high-dose (Group 4) did not contain any morphologic abnormality that was a direct result of 1,2,4-Trichlorobenzene administration. At necropsy, the percent of mice noted to have pale areas of the kidneys in Groups 1, 2, 3, and 4 was 0, 0, 14, and 40%, respectively, in the males; and 2, 0, 10, and 24%, respectively, in the females. However, there were no treatment-related histomorphologic abnormalities in the kidneys from the high-dose (Group 4) compared to the controls. Although the testes were noted at necropsy to be small in only 3/50 high-dose males, the absolute and relative (to body weight and to brain weight) mean organ weight values for the testes were significantly decreased in the high-dose males. At necropsy, the percent of males noted to have small seminal vesicles in Groups 1, 2, 3, and 4 was 0, 2, 4, and 40%, respectively. The testes and seminal vesicles were examined microscopically from all males in the control, mid-, and high-dose (Groups 1, 3, and 4). For Groups 1, 3, and 4, the percent of males exhibiting degeneration (either uni- or bilateral) of the testes was 2, 6, and 20%, respectively; and the percent exhibiting decreased secretion (bilateral) in the seminal vesicles was 0, 2, and 53%, respectively. In the conspicuous absence of a dose-response relationship, the degenerative changes evident in the testes and seminal vesicles of the high-dose males were most probably a secondary effect, resulting from the prolonged and severe cachectic state in the high-dose males caused by the liver neoplasia. At necropsy, the adrenals did not appear to be abnormal (enlarged adrenals in one high-dose female was the only abnormality noted). However, the adrenals were examined microscopically from all mice in the control, mid-, and high-dose groups. For Groups 1, 3, and 4, the percent of mice exhibiting adrenal degeneration/necrosis was 26, 12, and 51%, respectively, in the males; and 90, 86, and 54%, respectively, in the females; and the percent exhibiting adrenal congestion/hemorrhage was 10, 2, and 45%, respectively, in the males; and 32, 46, and 50%, respectively, in the females. As a result of

age- and sex-related hormonal changes, the adrenal glands of aging normal mice, especially females, typically exhibit congestion and degenerative changes within the inner cortical region, resulting in hemorrhage and congestion in the more severe cases. Unlike the majority of mice in Groups 1, 2, and 3, that were exsanguinated just prior to necropsy at study termination, almost all of the mice in Group 4 died during the study, and therefore were necropsied without prior exsanguination, resulting in an artifactual presence of adrenal congestion/hemorrhage and degenerative changes. In the absence of a dose-response relationship, histomorphologic abnormalities in the adrenals of the Group 4 mice were not a direct effect of 1,2,4-Trichlorobenzene administration.

In conclusion, in B6C3F1 male and female mice, the no-observed-effect-level (NOEL) of 1,2,4-Trichlorobenzene for carcinogenicity was 150 ppm; and the no-observed-adverse-effect-level (NOAEL) for systemic toxicity was 150 ppm. Compared to the controls, the incidence of hepatocellular carcinomas was increased in the mid- (700 ppm) and high-dose (3200 ppm) males and females. In the low-dose (150 ppm) mice, the incidence of hepatocellular neoplasia was not increased compared to the controls. Although there was no detectable histopathological correlate, liver mean weight values were significantly increased in the 150 ppm males and females; and mean liver-to-body-weight and liver-to-brain-weight values were significantly increased in the 150 ppm females.

HAZLETON WASHINGTON

SIGNATURE PAGE

Study Director:

Michael R. Moore — June 6, 1994

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Associate Toxicologist:

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HAZLETON WASHINGTON

CLINICAL PATHOLOGY REPORT

Summary

The test material, 1,2,4-Trichlorobenzene, was administered to mice at dietary levels of 0, 150, 700, and 3200 ppm (Groups 1-4, respectively) for at least 104 weeks. Blood smears were collected from all groups and examined for Groups 1, 3, and 4 at Weeks 52 and 104 and Groups 1 and 4 at Week 78 for determination of relative differential leukocyte counts and cellular morphology. There was no evidence of leukemia in the control or treated animals.

Results and Discussion

Hematology - Based upon evaluation of the blood smears, the absolute leukocyte counts were estimated to be within normal limits for most animals; the significant changes observed in the relative differential leukocyte counts were of low magnitude and considered of no biologic or toxicologic importance. The mean values for percentage segmented neutrophils were significantly increased in Group 3 animals but decreased in Group 4 animals at Week 52 and significantly increased in Group 4 males at Week 105. Mean percentage lymphocyte values were significantly decreased in Group 3 animals and increased in Group 4 animals at Week 52 and significantly decreased in Group 4 males at Week 105. Significant decreases were observed in the mean values for percentage monocytes in Group 4 females at Week 52 and eosinophils in Group 4 males at Week 52, Group 4 animals at Week 78, and Group 3 females at Week 105. The aforementioned changes are considered to be incidental to the administration of the test material.

The incidence of echinocytosis was slightly increased in Group 4 males at Weeks 52, Group 4 animals at Week 78, and Group 3 animals and Group 4 males at Week 105. The incidence of acanthocytes was increased in Group 4 females at Week 78. Echinocytosis may be observed as an artifact

of blood film preparation and is not specific for a pathologic process; acanthocytosis is a rather nonspecific finding but is seen in animals with liver, spleen, or kidney disease.

Unscheduled Deaths - There was no evidence of an effect of the test material on the relative differential leukocyte counts or cellular morphology for moribund-sacrifice animals.

Clinical Pathologist:

Renée C. Pearson — June 2, 1994

Renée C. Pearson, M.S., D.V.M., Date
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PATHOLOGY REPORT

Four groups of B6C3F1/CrlBr/Charles River mice were each exposed to 1,2,4-Trichlorobenzene at one of four dose levels defined as follows: Group 1 - vehicle control (50 males, 50 females), 0 mg/kg/day; Group 2 - low (50 males, 50 females), 150 mg/kg/day; Group 3 - mid (50 males, 50 females), 700 mg/kg/day; Group 4 - high (50 males, 50 females), 3200 mg/kg/day. Exposure was via the diet for a period of approximately 104 weeks, after which all surviving animals were sacrificed for pathologic evaluation. Evaluation of those animals (including any sacrificed in extremis or dying prior to the scheduled sacrifice) is the subject of this report.

Methods

All surviving animals were sacrificed, at the appropriate time, by exsanguination under barbiturate anesthesia, and all were subjected to a necropsy examination. All surviving animals were weighed once prior to the initiation of exposure, weekly during Weeks 1-16, and once every four weeks thereafter, including just prior to necropsy.

Clinical observations were reviewed at necropsy, and all grossly observed abnormalities were entered directly into the computerized data capture system. Kidneys, brain (with brainstem), and testes (with epididymides) were weighed from 10 animals/sex/group. Liver (with gallbladder) was weighed from all animals sacrificed on Days 1, 3, and 4 of the terminal sacrifice.

After gross examination, appropriate samples of each of the following organs/tissues were preserved in 10% neutral-buffered formalin:

masses and associated tissues
gross lesions
brain with brainstem
(medulla/pons, cerebellar cortex, and cerebral cortex)
seminal vesicles
ovaries
uterus with vagina and cervix
mammary gland (females only)
skin

pituitary
thyroid (with parathyroids)
thymus
trachea
lungs
heart
salivary glands (mandibular)
liver (with gallbladder)
spleen
kidneys
adrenals
pancreas
testes with epididymides
prostate
esophagus
stomach
duodenum, jejunum, ileum
colon, cecum, rectum
urinary bladder
mesenteric lymph node
mandibular lymph node
sciatic nerve
cervical spinal cord
mid-thoracic spinal cord
lumbar spinal cord
femur with bone marrow
skeletal muscle (thigh)
eyes (with Harderian glands)

After fixation, all bony tissues were decalcified prior to processing. Tissues to be examined histologically were embedded in paraffin, sectioned at 5 μ, and stained with hematoxylin and eosin.

As required by the protocol, histologic evaluations were conducted on those tissues listed above from all animals of Groups 1 and 4 sacrificed at the terminal point of the study and from any animals dying or sacrificed in extremis prior to the scheduled sacrifice. Gross lesions were examined from all animals regardless of exposure level. The liver was identified as a possible target organ during the initial histopathological evaluations and was then, as required by the protocol, examined histologically from all remaining animals. In addition, adrenal cortex, testes, and seminal vesicles were examined from Group 3 animals in order to help define any possible relationship between certain changes encountered in these organs during initial histologic examination, and exposure to the test substance. All histologic findings were entered directly into the computerized data capture system. Most nontumor lesions were graded as to relative severity or degree of involvement (1 = minimal, 2 = slight, 3 = moderate, 4 = moderately severe, 5 = severe). The grades are subjective, comparative evaluations, based on morphology alone, and are not intended by themselves to imply any degree of functional impairment.

Gross and Related Findings

Gross findings are summarized in detail in the tables and appendices.

Survival was drastically reduced in males and females of Group 4 compared to other exposure groups. Only 5/50 males and 0/50 females of Group 4 survived to termination, compared to survival rates that ranged from 74 to 90% in all other sex/dose groups (higher survival in males). Most of the deaths in Group 4 occurred as a result of hepatocellular carcinomas, many of which were large and observed grossly.

Mean terminal body weights may have been affected by exposure to 1,2,4-Trichlorobenzene, but interpretation of terminal weight values alone is confounded by the lack of survival at the highest dose level. However, mean body weights were significantly depressed in Group 4 animals of both sexes for the duration of the study, starting with the first week of exposure. In other groups, body weights were inconsistent compared to controls, but were frequently increased over the duration of the study.

Food consumption was less consistently affected, being generally depressed in Group 4 for the first 55 to 60 weeks, but then rebounding to become increased relative to controls for the remainder of the study. This rebound phenomenon is difficult to explain; nevertheless, body weights did not rebound with the increased food consumption, a condition explainable by the severe pathology present in animals of Groups 3 and 4.

Terminal organ weight data were also clouded by high mortality in Group 4 animals; however, a number of observations are important.

Mean terminal liver weights were significantly increased in males of Groups 2, 3, and 4 and females of Groups 2 and 3 (all Group 4 females died prior to termination). This occurred partly as a result of liver tumors (many of them very large) which were present in increased numbers in males and females of Groups 3 and 4 and partly because of another less obvious alteration observed histologically, which will be described later in this report.

Mean terminal testicular weights appear to have been significantly depressed in Group 4 males compared to all other groups. There was no clear histologic correlate, but the histologic data do suggest an increase in the degree of degenerative changes within the testes of Group 4 animals.

The most commonly described gross abnormalities were masses, enlargements, or irregularities of contour within the liver. Seen mostly in males and females of Group 4 and indicative of an effect of exposure to the test substance, most of these lesions were subsequently shown histologically to be hepatocellular carcinomas. It was common for these neoplasms to be accompanied by grossly noted accumulations of ascitic fluid.

"Lumen, material" was frequently described within the glandular stomach of many terminal-sacrifice animals without relation to dose. This was the result of mice licking their tail after the tip had been amputated for blood collection and not reflective of any lesion of the stomach itself.

Cysts were frequently observed grossly within the ovaries and uterus of female mice without relation to exposure. Both are common, age-related lesions that occur in laboratory mice of this and other strains as a result of endocrine senescence.

"Pale area" was noted in the kidneys of Group 4 animals of both sexes at a higher incidence than any other exposure groups. There was no specific histologic correlate.

Histopathology

Histologic findings are summarized in the tables and appendices.

There was a large (and significant) increase in the incidence of hepatocellular carcinomas in males and females of Groups 3 and 4 compared to the other groups. Hepatocellular carcinomas were present in 100% of examined Group 4 males, 92% of Group 4 females, 54% of Group 3 males, and

56% of Group 3 females. In no other group did the incidence exceed 16%. The tumors were mostly large and often multiple, frequently with pulmonary metastases. Architecturally, the carcinomas were heterogeneous, often characterized by some degree of trabeculation. Adenomas were also increased in incidence in the same groups (except for Group 4 males, in which they were likely overwhelmed by the extent of carcinoma development), but were smaller and more circumscribed, with less architectural and cytologic variation. Necrosis, often present within the neoplasms and in the adjoining parenchyma, was mostly interpreted as secondary to the neoplasia.

Also present within liver tissue, and clearly associated directly with 1,2,4-Trichlorobenzene exposure, was enlargement of hepatocytes within the centrilobular zone of livers from many males of Groups 3 and 4, including animals with and without concurrent hepatic neoplasia. Hepatocytic cytoplasm within affected areas appeared slightly more dense and eosinophilic than normal. This change, when seen, is often associated with increased liver weights.

Other hepatic alterations, including focal necrosis, portal inflammation and fibrosis, and regenerative changes were also related to exposure to the test substance, but were likely secondary to or influenced by the severe degree of hepatic neoplasia present in these animals.

None of the other observed histologic changes were clearly attributable to 1,2,4-Trichlorobenzene exposure.

A number of spontaneous lesions that are normally increased as mice of this strain age were seen less frequently in animals of Group 4 as a result of the very high mortality that occurred in both males and females at that exposure level. Included in this group of lesions were focal mineralization within the thalamic region of the brain, development of peribronchial/perivascular lymphoid aggregates within the lungs, lesions of chronic progressive nephropathy, and development of ovarian cysts and uterine cystic endometrial hyperplasia.

The adrenal glands of aging mice, mostly female, frequently exhibited congestion and degenerative changes within the inner cortical region, resulting in hemorrhage and necrosis in the more severe cases. In addition, many of these glands showed varying degrees of hyperplasia of the subcapsular spindle-cell population. These changes are all hormonally related to age and sex and are expected in normal mice of this age and strain. They are not restricted entirely to females, but the degenerative changes, especially, are generally much more pronounced in that sex. That pattern was true for this study; however, in males, there was the impression of increased congestion/hemorrhage and degenerative changes within the corticomedullary region of the adrenals in animals of Group 4 compared to control. It is important to consider, however, that many Group 4 males died and were necropsied without exsanguination, and in many of these autolysis within this anatomic area was considerable. Given the complete absence of a dose response, as demonstrated by the lack of any increase in the incidence of these lesions in Group 3 animals of either sex, it is very likely that the observed increase in degenerative changes recorded for this area was artifactual rather than any direct effect of exposure to the test substance.

The seminal vesicles of Group 4 males often appeared empty and contracted; there was also an increase in the observed incidence of degenerative changes within testicular seminiferous tubules. Group 3 animals were not affected. While these changes are compatible with a toxic effect, they are also characteristic of prolonged cachectic and terminal disease processes in which normal physiologic activities are often severely affected. The latter explanation seems probable in light of the conspicuous lack of dose response and the severe and fatal debilitation suffered by animals of Group 4.

All other histologic changes were comparably distributed between examined groups and of the types and general frequencies usually encountered in normal populations of mice of this strain and age.

Discussion and Conclusions

Dietary exposure of B6C3F1 mice to 1,2,4-Trichlorobenzene for 2 years, or until death intervened, resulted in the induction of liver tumors (mostly hepatocellular carcinomas, but also significant numbers of adenomas) in males and females of Groups 3 and 4. Because liver was shown early in the study to be a target organ, all livers were examined histologically; thus, the relatively low incidence of liver tumors at the Group 2 level (comparable to control incidences) would suggest that there was no hepatocarcinogenic effect of exposure at that level.

Centrilobular hepatocellular hypertrophy was also seen in males of Groups 3 and 4 as a direct result of exposure to the test substance.

Group 4 survival was very poor. All females and all but five males of that group died or were sacrificed in extremis prior to the study's termination, and the pattern of early death became evident quite early - at approximately 65 to 70 weeks into the study for both sexes - and progressed at a rapid rate for the remainder of the study.

Comprehensive histopathologic evaluations were performed routinely only on animals of Groups 1 and 4. Tissues other than liver from animals of Groups 2 and 3 (in which survival was excellent) and adrenal cortex, testes and seminal vesicles from animals of Group 3 were not examined histologically except from the relatively few animals of those groups dying early or unless grossly abnormal; consequently, most of the tissues examined from animals exposed to the test substance were from animals that died early. Except for liver, adrenal cortex, testes, and seminal vesicles then, there were relatively few tissues of any kind examined from animals exposed to the test substance for the entire 104 week exposure period. While little can be said of the status of those tissues from animals of Groups in which they were unexamined, it seems reasonably well established that those "degenerative lesions" observed with greater frequency in adrenal cortex, testes, and seminal vesicles of Group 4 animals were partially secondary to the prolonged and severe

cachectic disease that resulted in the death of so many animals of that group and partially artifactual (a result of the lack of exsanguination in autolyzed tissues). There is no evidence that they occurred from direct toxic effects of 1,2,4-Trichlorobenzene.

Pathologist:

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Table 10C
Histopathology Incidence Summary - All Deaths
104-Week Dietary Carcinogenicity Study with 1,2,4-Trichlorobenzene in Mice

Key to Table 10C Histopathology Incidence Summary

SYMBOLS PREFACING NEOPLASTIC FINDINGS

B- = Primary, Benign Neoplasm
M- = Primary, Malignant Neoplasm
N- = Metastatic Neoplasm
X- = Other Neoplasm

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=ALL;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER OF ANIMALS AFFECTED ---							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	50	50	50	50	50	50	50	50
** TOP OF LIST **									
BRAIN W/STEM (BR)	NUMBER EXAMINED:	50	7	9	50	50	15	8	50
	NOT REMARKABLE:	13	5	3	33	23	9	5	37
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	1	0	0	0	0	0
--MINERALIZATION, FOCAL, THALAMUS		36	2	5	16	27	3	2	13
--DILATED VENTRICLE(S)		1	0	0	0	0	0	0	0
--HEMORRHAGE, FOCAL		0	0	0	0	0	0	1	0
--MALACIA, FOCAL		0	0	0	0	0	1	0	0
--GLIOSIS, FOCAL		0	0	0	0	0	1	0	0
--LYMPHOCYTIC INFILTRATE, MENINGES		0	0	0	0	1	0	0	0
--VENTRAL COMPRESSION		0	0	0	0	1	1	0	0
--AUTOLYZED		0	0	0	1	0	1	0	0
CORD, CERVICAL (CS)	NUMBER EXAMINED:	50	7	9	50	50	13	8	50
	NOT REMARKABLE:	50	7	8	49	49	12	8	50
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	1	0	0	0	0	0
--LYMPHOCYTIC INFILTRATE, MENINGES		0	0	0	0	1	0	0	0
--AUTOLYZED		0	0	0	1	0	1	0	0
CORD, THORACIC (TC)	NUMBER EXAMINED:	50	7	9	50	50	13	8	50
	NOT REMARKABLE:	50	7	8	49	49	12	8	50
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	1	0	0	0	0	0
--LYMPHOCYTIC INFILTRATE, MENINGES		0	0	0	0	1	0	0	0
--AUTOLYZED		0	0	0	1	0	1	0	0
CORD, LUMBAR (LC)	NUMBER EXAMINED:	50	7	9	50	50	13	8	50
	NOT REMARKABLE:	50	7	7	49	49	12	8	50
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	1	0	0	0	0	0
--LYMPHOCYTIC INFILTRATE, MENINGES		0	0	0	0	1	0	0	0
--AUTOLYZED		0	0	1	1	0	1	0	0

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=ALL;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER OF ANIMALS AFFECTED ---							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	50	50	50	50	50	50	50	50
PITUITARY (PI)	NUMBER EXAMINED:	50	7	9	50	50	15	10	50
	NOT REMARKABLE:	43	5	7	41	38	12	8	46
--B-ADENOMA		0	0	0	0	5	2	0	0
--CYST(S)		3	0	0	0	0	0	0	0
--HYPERPLASIA, FOCAL		1	0	0	0	4	0	1	0
--HEMATOCYST		0	0	0	0	1	0	0	0
--ANGIECTASIS		0	0	0	0	0	0	1	0
--AUTOLYZED		0	0	0	1	0	0	0	0
--MISSING		3	2	2	8	2	1	0	4
ADRENAL, CORTEX (AC)	NUMBER EXAMINED:	50	7	50	50	50	13	50	50
	NOT REMARKABLE:	1	0	3	7	1	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	3	0	2	1	1	0
--B-ADENOMA		5	1	1	0	1	0	0	0
--HYPERPLASIA, SUBCAPSULAR CELL		44	7	45	22	49	13	48	44
--DEGENERATION/NECROSIS, CORTICOMEDULLARY JUNCTION		13	0	6	25	45	9	43	27
--CONGESTION/HEMORRHAGE, CORTICOMEDULLARY JUNCTION		5	0	1	22	16	2	23	25
--NECROSIS, UNILATERAL		0	0	0	1	0	0	0	0
--NECROSIS, BILATERAL		0	0	0	0	0	1	0	0
--HYPERTROPHY, FOCAL		14	1	10	0	1	0	0	0
--HYPERPLASIA, FOCAL		2	0	1	0	0	0	0	0
--AMYLOIDOSIS		0	0	0	0	0	0	0	1
--LIPOIDOSIS, FOCAL		0	0	0	0	0	0	2	0
--VACUOLIZATION, C-M JUNCTION		0	0	0	0	0	0	2	0
--HYPERTROPHY, DIFFUSE		0	0	0	0	0	0	1	0
--AUTOLYZED		1	0	0	1	0	0	0	0
ADRENAL, MEDULLA (AM)	NUMBER EXAMINED:	50	7	50	50	50	13	50	50
	NOT REMARKABLE:	49	7	49	47	50	13	50	50
--B-BENIGN PHEOCHROMOCYTOMA		0	0	1	0	0	0	0	0
--AUTOLYZED		1	0	0	1	0	0	0	0
--MISSING		0	0	0	2	0	0	0	0

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=ALL;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION	SEX:	MALE				FEMALE			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	50	50	50	50	50	50	50	50
THYROID (TY)	NUMBER EXAMINED:	50	7	9	50	50	13	8	50
	NOT REMARKABLE:	45	7	8	46	46	13	8	45
--B-FOLLICULAR CELL ADENOMA		2	0	0	1	2	0	0	0
--M-FOLLICULAR CELL CARCINOMA		0	0	0	0	1	0	0	0
--M-"C" CELL CARCINOMA		0	0	0	1	0	0	0	0
--AMYLOIDOSIS		0	0	0	0	0	0	0	1
--CYSTIC FOLLICLE(S)		1	0	0	0	0	0	0	0
--AUTOLYZED		1	0	1	2	0	0	0	0
--MISSING		1	0	0	0	1	0	0	0
PARATHYROID (PT)	NUMBER EXAMINED:	50	7	9	50	50	13	8	50
	NOT REMARKABLE:	38	7	8	40	43	9	7	45
--AMYLOIDOSIS		0	0	0	0	0	0	0	1
--CYST(S)		0	0	1	0	0	1	1	0
--HYPERPLASIA, FOCAL		0	0	0	0	1	0	0	0
--AUTOLYZED		1	0	0	2	0	0	0	0
--MISSING		11	0	0	8	6	3	0	4
ESOPHAGUS (ES)	NUMBER EXAMINED:	50	7	9	50	50	13	8	50
	NOT REMARKABLE:	50	7	9	50	47	12	8	50
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	2	0	0	0
--MISSING		0	0	0	0	1	1	0	0
TRACHEA (TR)	NUMBER EXAMINED:	50	7	9	49	50	13	8	50
	NOT REMARKABLE:	50	7	9	49	49	12	8	50
--AUTOLYZED		0	0	0	1	0	0	0	0
--MISSING		0	0	0	0	1	1	0	0
LUNG (LU)	NUMBER EXAMINED:	50	8	12	50	50	15	11	50
	NOT REMARKABLE:	4	2	2	13	0	1	0	9
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	1	2	0	5	4	3	0
--B-ALVEOLAR/BRONCHIOLAR ADENOMA		3	0	1	2	0	0	0	1

** CONTINUED ON NEXT PAGE **

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=ALL;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		---NUMBER-OF-ANIMALS-AFFECTED---							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	50	50	50	50	50	50	50	50
** FROM PREVIOUS PAGE **									
LUNG (LU)	NUMBER EXAMINED:	50	8	12	50	50	15	11	50
	NOT REMARKABLE:	4	2	2	13	0	1	0	9
--M-ALVEOLAR/BRONCHIOLAR CARCINOMA		3	1	3	0	3	1	1	0
--M-HEPATOCELLULAR CARCINOMA, METASTATIC		1	0	0	11	0	0	0	8
--M-KUPFFER CELL SARCOMA		0	0	0	1	0	0	0	0
--M-SARCOMA, METASTATIC, PRIMARY UNKNOWN		0	0	0	1	0	0	0	0
--M-OSTEOSARCOMA, METASTATIC, PRIMARY UNKNOWN		0	0	0	0	0	0	1	0
--M-FIBROSARCOMA, METASTATIC		0	0	1	0	0	0	0	0
--PERIBRONCHIAL/PERIVASCULAR, INFILTRATION, LYMPHOID		40	5	6	17	44	9	7	23
--CONGESTION/HEMORRHAGE, AGONAL		3	1	2	22	3	1	2	18
--FOAM-CELL FOCUS(I)		1	0	0	2	0	0	0	4
--INFLAMMATION, CHRONIC, FOCAL		1	0	1	1	3	0	2	1
--INFLAMMATION, SUBACUTE, TUMOR ASSOCIATED		1	0	0	0	0	0	0	0
--INFLAMMATION, CHRONIC, PLEURA		1	0	0	0	1	0	0	0
--HYPERPLASIA, HILAR LYMPH NODE		0	0	0	0	0	0	0	1
--HYPERPLASIA, ALVEOLAR CELL		2	0	0	0	1	0	0	0
--PIGMENT LADEN MACROPHAGES		1	0	0	0	0	0	0	0
--ALVEOLAR HISTIOCYTOSIS		1	1	0	0	0	0	2	0
HEART (HT)	NUMBER EXAMINED:	50	7	9	50	50	13	8	50
	NOT REMARKABLE:	49	7	8	47	48	10	7	48
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	1	0	1	0	0	0
--FIBROSIS, MYOCARDIUM		0	0	0	2	0	0	0	0
--AMYLOIDOSIS		0	0	0	0	0	0	0	1
--DEGENERATION, MYOCARDIUM		1	0	0	1	1	2	1	1
--INFLAMMATION, CHRONIC, FOCAL		0	0	0	0	0	1	0	0
LIVER (LI)	NUMBER EXAMINED:	50	50	50	50	50	50	50	50
	NOT REMARKABLE:	25	16	0	0	7	9	2	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	3	4	1	6	12	3	0
--B-HEPATOCELLULAR ADENOMA		4	7	16	2	3	4	16	8
--M-HEPATOCELLULAR CARCINOMA		8	5	27	50	1	1	28	46
--M-KUPFFER CELL SARCOMA		0	0	0	1	0	0	1	0

** CONTINUED ON NEXT PAGE **

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=ALL;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION	--- NUMBER OF ANIMALS AFFECTED ---							
SEX:	-------MALE-------				------FEMALE------			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
NUMBER:	50	50	50	50	50	50	50	50
** FROM PREVIOUS PAGE **								
LIVER (LI) ..... NUMBER EXAMINED:	50	50	50	50	50	50	50	50
NOT REMARKABLE:	25	16	0	0	7	9	2	0
--M-HEMANGIOSARCOMA	2	0	0	0	1	0	0	0
--M-OSTEOSARCOMA, METASTATIC, PRIMARY UNKNOWN	0	0	0	0	0	0	1	0
--HEPATOCYTOMEGALY, CENTRILOBULAR	0	0	27	20	0	0	1	8
--INFLAMMATION, CHRONIC, FOCAL	7	18	7	1	36	25	25	2
--FIBROSIS, PORTAL	0	0	0	2	0	0	0	0
--INFLAMMATION, CHRONIC ACTIVE, PORTAL	0	0	0	4	0	0	1	2
--NECROSIS, FOCAL	0	0	3	3	0	1	2	7
--NECROSIS, SINGLE CELL	0	0	0	1	0	0	0	0
--HYPERPLASIA, OVAL CELL	0	0	0	1	0	0	0	0
--HYPERPLASIA, REGENERATIVE	0	0	0	2	0	0	0	0
--HYPERPLASIA, KUPFFER CELL, FOCAL	0	0	0	0	1	0	0	0
--LIPOIDOSIS, MIDZONAL	1	4	0	3	0	0	0	0
--LIPOIDOSIS, FOCAL	0	0	0	0	0	1	0	0
--CELLULAR ALTERATION, EOSINOPHILIC	0	0	0	0	0	0	1	0
--CELLULAR ALTERATION, CLEAR	1	2	0	0	1	0	0	0
--CELLULAR ALTERATION, GROUND GLASS	3	1	0	0	0	0	0	0
--CELLULAR ALTERATION, BASOPHILIC	0	1	0	0	0	0	1	0
--EXTRAMEDULLARY HEMATOPOIESIS, INCREASED	1	0	0	0	0	2	0	0
--HEMATOCYST, TUMOR ASSOCIATED	0	0	0	0	0	0	1	8
--INFARCTED NODULE	0	0	0	2	1	0	1	0
--AMYLOIDOSIS	0	0	0	0	0	0	0	1
--BILE DUCT, CYST	0	1	0	0	0	0	0	0
--DEGENERATION, CYSTIC	0	1	0	0	0	0	0	0
--AUTOLYZED	1	0	0	0	0	0	0	0
GALLBLADDER (GB) ..... NUMBER EXAMINED:	50	7	9	50	50	13	8	50
NOT REMARKABLE:	41	3	4	8	41	7	2	12
--INSPISSATED, MINERALIZED BILE	0	0	0	1	0	0	0	0
--AUTOLYZED	4	0	3	17	6	5	3	18
--MISSING	5	4	2	24	3	1	3	20

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=ALL;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		MALE -1-	MALE -2-	MALE -3-	MALE -4-	FEMALE -1-	FEMALE -2-	FEMALE -3-	FEMALE -4-
	NUMBER:	50	50	50	50	50	50	50	50
KIDNEY (KD)	NUMBER EXAMINED:	50	17	17	50	50	14	15	50
	NOT REMARKABLE:	1	1	1	30	36	9	6	33
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	2	0	2	3	1	0
--B-BENIGN TUBULE CELL ADENOMA		1	0	0	0	0	0	0	0
--M-MALIGNANT TUBULE CELL CARCINOMA		0	0	0	0	1	0	0	0
--NEPHROPATHY, CHRONIC PROGRESSIVE		42	11	10	5	7	2	6	6
--TUBULE, MINERALIZATION		45	12	9	9	2	0	2	5
--TUBULE CELLS, PROTEIN RESORPTION DROPLETS		1	1	1	0	1	0	0	0
--HYPERPLASIA, TUBULAR EPITHELIUM		0	0	0	2	0	0	0	0
--PYELONEPHRITIS		1	2	2	1	0	0	0	0
--AMYLOIDOSIS		0	0	0	1	2	0	0	1
--PIGMENT, PROXIMAL TUBULES		0	0	0	3	0	0	1	4
--PELVIS, DILATATION		1	0	0	0	0	0	0	1
--PELVIS, CALCULUS		0	0	0	0	0	0	1	0
--CYST		5	1	1	3	0	0	0	0
--METAPLASIA, OSSEOUS		1	0	0	0	0	0	0	1
--MINERALIZATION, CAPSULE		0	0	0	1	0	0	0	0
--HYDRONEPHROSIS, UNILATERAL		0	0	0	0	0	0	1	0
--MAST CELL INFILTRATE		0	1	0	0	0	0	0	0
--AUTOLYZED		1	0	0	1	0	0	0	2
SPLEEN (SP)	NUMBER EXAMINED:	50	9	11	50	50	22	17	50
	NOT REMARKABLE:	42	3	5	46	38	6	5	48
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	3	4	0	6	11	6	0
--M-HEMANGIOSARCOMA		2	1	0	1	0	0	3	0
--EXTRAMEDULLARY HEMATOPOIESIS, INCREASED		1	1	2	1	3	3	0	0
--PIGMENT, INCREASED		0	1	0	0	2	0	1	0
--CONGESTION/HEMORRHAGE		1	0	1	0	0	0	0	0
--HYPERPLASIA, LYMPHOID		1	0	0	0	3	2	2	0
--AUTOLYZED		1	0	0	2	0	0	0	2
--MISSING		0	0	0	0	0	0	1	0

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=ALL;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION	SEX:	MALE				FEMALE			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	50	50	50	50	50	50	50	50
STOMACH, NONGL (SU) ..... NUMBER EXAMINED:		50	7	10	50	50	13	10	50
NOT REMARKABLE:		47	6	7	47	46	10	8	48
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	1	0	1	0	0	0
--B-SQUAMOUS CELL PAPILLOMA		0	0	0	0	0	0	1	0
--HYPERKERATOSIS		0	0	1	0	0	1	0	1
--HEMORRHAGE, RETICULARIS		0	0	0	1	0	0	0	0
--MAST CELL INFILTRATE		0	1	0	0	0	0	0	0
--AUTOLYZED		2	0	0	2	3	2	1	1
--MISSING		1	0	1	0	0	0	0	0
STOMACH, GL (ST) ..... NUMBER [illegible]INED:		50	7	11	50	[illegible]		9	50
NOT REMARKABLE:		47	5	6	45	[illegible]			47
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	2	0	3	[illegible]	0	0
--ULCER		0	0	1	1	1	1	0	1
--AMYLOIDOSIS		0	0	0	0	0	0	0	1
--EROSION		0	1	1	1	1	1	0	0
--MINERALIZATION, FOCAL, MUCOSA		0	0	0	0	1	0	0	0
--AUTOLYZED		2	1	1	3	3	2	1	1
--MISSING		1	0	0	0	0	0	0	0
DUODENUM (DU) ..... NUMBER EXAMINED:		50	8	9	50	50	14	9	50
NOT REMARKABLE:		47	5	5	25	43	6	5	27
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	1	1	1	0
--M-CARCINOMA		0	1	0	0	1	0	0	0
--AMYLOIDOSIS		0	0	0	0	0	0	0	1
--AUTOLYZED		3	1	4	25	5	7	3	21
--MISSING		0	1	0	0	0	0	0	1
JEJUNUM (JE) ..... NUMBER EXAMINED:		50	7	9	50	50	13	8	50
NOT REMARKABLE:		46	6	5	18	44	6	4	21
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	0	0	0	0	0	0
--AMYLOIDOSIS		0	0	0	0	0	0	0	1
--AUTOLYZED		3	1	4	32	6	7	4	28

TABLE 10C
104-WEEK DIETARY CARCINOGENICITY STUDY WITH
1,2,4-TRICHLOROBENZENE IN MICE
HISTOPATHOLOGY INCIDENCE SUMMARY

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=ALL;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	50	50	50	50	50	50	50	50
ILEUM (IL)	NUMBER EXAMINED:	50	7	9	50	50	13	8	50
	NOT REMARKABLE:	46	6	5	22	43	5	5	20
--AUTOLYZED		4	1	4	28	6	7	3	29
--MISSING		0	0	0	0	1	1	0	1
PANCREAS (PA)	NUMBER EXAMINED:	50	7	9	50	50	13	8	50
	NOT REMARKABLE:	45	7	5	43	45	8	7	47
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	3	0	3	1	0	0
--B-ISLET CELL ADENOMA		1	0	0	0	0	0	0	0
--CYTOPLASMIC CHANGE, EOSINOPHILIC		1	0	0	0	0	0	0	0
--CYSTIC DUCT(S)		0	0	0	0	1	0	0	1
--ATROPHY, ACINAR CELL		1	0	0	0	0	0	0	0
--AUTOLYZED		1	0	1	5	0	2	1	2
--MISSING		0	0	0	2	1	2	0	0
CECUM (CE)	NUMBER EXAMINED:	50	7	9	50	50	13	8	50
	NOT REMARKABLE:	48	4	5	29	43	6	5	25
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	2	0	1	0	0	0
--AUTOLYZED		2	3	2	21	6	6	3	24
--MISSING		0	0	0	0	0	1	0	1
COLON (CO)	NUMBER EXAMINED:	50	7	9	50	50	13	8	50
	NOT REMARKABLE:	48	5	6	40	48	11	7	42
--AUTOLYZED		2	2	2	10	2	2	1	7
--MISSING		0	0	1	0	0	0	0	1
RECTUM (RE)	NUMBER EXAMINED:	50	7	9	50	50	13	8	50
	NOT REMARKABLE:	49	5	8	40	46	10	7	43
--BLOC. FILLED		0	1	0	0	0	0	0	0
--AUTOLYZED		1	1	1	10	2	3	1	6
--MISSING		0	0	0	0	0	0	0	1

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=ALL;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER OF ANIMALS AFFECTED ---							
	SEX:	MALE				FEMALE			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	50	50	50	50	50	50	50	50
LN, MESENTERIC (MS)	NUMBER EXAMINED:	50	11	14	50	50	20	12	50
	NOT REMARKABLE:	28	3	2	24	39	5	4	31
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		4	4	7	0	5	12	3	0
--M-HEMANGIOSARCOMA		0	0	0	2	0	0	0	1
--CONGESTION/HEMORRHAGE		16	2	4	10	3	0	4	13
--HYPERPLASIA, LYMPHOID		0	0	0	0	1	0	1	0
--AUTOLYZED		1	0	0	1	2	1	0	0
--MISSING		1	2	1	13	1	3	0	5
TESTIS (TE)	NUMBER EXAMINED:	50	7	50	50	0	0	0	0
	NOT REMARKABLE:	49	7	46	40	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	1	0	0	0	0	0
--DEGENERATION, UNILATERAL		1	0	3	1	0	0	0	0
--DEGENERATION, BILATERAL		0	0	0	9	0	0	0	0
EPIDIDYMIS (EP)	NUMBER EXAMINED:	50	7	9	50	0	0	0	0
	NOT REMARKABLE:	49	7	6	48	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	2	0	0	0	0	0
--M-SCHWANNOMA		0	0	1	0	0	0	0	0
--HYPOSPERMIA		0	0	0	1	0	0	0	0
--AUTOLYZED		1	0	0	1	0	0	0	0
PROSTATE (PR)	NUMBER EXAMINED:	50	7	9	50	0	0	0	0
	NOT REMARKABLE:	49	7	6	41	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	2	0	0	0	0	0
--ATROPHY		0	0	0	2	0	0	0	0
--INFLAMMATION, SUBACUTE		0	0	1	0	0	0	0	0
--AUTOLYZED		0	0	0	5	0	0	0	0
--MISSING		0	0	0	2	0	0	0	0

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=ALL;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION	--- NUMBER OF ANIMALS AFFECTED ---							
SEX:	MALE				FEMALE			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
NUMBER:	50	50	50	50	50	50	50	50
SEMINAL VESICLE (SV) ..... NUMBER EXAMINED:	50	11	50	50	0	0	0	0
NOT REMARKABLE:	41	9	44	21	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)	1	0	2	0	0	0	0	0
--DECREASED SECRETION, BILATERAL	0	0	1	24	0	0	0	0
--DISTENDED	6	1	3	0	0	0	0	0
--AUTOLYZED	2	1	0	2	0	0	0	0
--MISSING	0	0	0	3	0	0	0	0
OVARY (OV) ..... NUMBER EXAMINED:	0	0	0	0	50	18	21	50
NOT REMARKABLE:	0	0	0	0	13	6	4	13
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)	0	0	0	0	2	1	1	0
--B-TERATOMA	0	0	0	0	0	1	0	0
--M-MALIGNANT GRANULOSA/THECA CELL TUMOR	0	0	0	0	0	0	1	1
--M-HEMANGIOSARCOMA	0	0	0	0	0	1	0	0
--M-HEPATOCELLULAR CARCINOMA, METASTATIC	0	0	0	0	0	0	0	1
--ATROPHY	0	0	0	0	22	2	4	28
--BURSA, CYST	0	0	0	0	2	0	4	1
--CYST(S)	0	0	0	0	17	4	13	4
--HEMATOCYST	0	0	0	0	12	5	4	0
--AUTOLYZED	0	0	0	0	0	1	0	0
--MISSING	0	0	0	0	0	0	0	5
UTERUS (UT) ..... NUMBER EXAMINED:	0	0	0	0	50	44	43	50
NOT REMARKABLE:	0	0	0	0	1	1	2	41
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)	0	0	0	0	1	0	0	0
--B-ENDOMETRIAL STROMAL POLYP	0	0	0	0	2	0	0	0
--B-HEMANGIOMA	0	0	0	0	0	1	0	0
--M-LEIOMYOSARCOMA	0	0	0	0	0	1	0	0
--M-ENDOMETRIAL STROMAL SARCOMA	0	0	0	0	1	0	0	0
--HYPERPLASIA, CYSTIC ENDOMETRIAL	0	0	0	0	47	41	40	3
--DILATATION	0	0	0	0	3	5	8	4
--AMYLOIDOSIS	0	0	0	0	1	1	0	1
--AUTOLYZED	0	0	0	0	2	1	0	0
--MISSING	0	0	0	0	0	0	0	1

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=ALL;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		---NUMBER-OF-ANIMALS-AFFECTED---							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	50	50	50	50	50	50	50	50
UTERUS, CERVIX (CV)	NUMBER EXAMINED:	0	0	0	0	50	14	9	50
	NOT REMARKABLE:	0	0	0	0	42	11	5	46
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	.	0	0	0
--M-SARCOMA		0	0	0	0	0	1	0	0
--M-HEMANGIOSARCOMA		0	0	0	0	0	0	1	0
--ENDOMETRIAL CYST(S)		0	0	0	0	1	0	1	2
--AUTOLYZED		0	0	0	0	0	1	1	0
--MISSING		0	0	0	0	3	1	2	2
VAGINA (VA)	NUMBER EXAMINED:	0	0	0	0	50	13	8	50
	NOT REMARKABLE:	0	0	0	0	49	11	7	48
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	1	0	0	0
--AUTOLYZED		0	0	0	0	0	1	1	0
--MISSING		0	0	0	0	0	1	0	2
URINARY BLADDER (UB)	NUMBER EXAMINED:	50	8	9	50	50	13	8	50
	NOT REMARKABLE:	48	7	6	37	46	9	6	42
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	2	0	2	0	0	0
--B-SCHWANNOMA		0	0	0	0	0	0	0	2
--INFLAMMATION, SUPPURATIVE		0	0	1	0	0	0	0	0
--INFLAMMATION, SUBACUTE		0	1	0	0	0	0	0	0
--HYPERPLASIA, EPITHELIAL		0	1	0	0	0	0	0	0
--AUTOLYZED		1	0	0	11	2	3	1	4
--MISSING		1	0	0	2	0	1	1	2
MAND SALIVARY GL (SG)	NUMBER EXAMINED:	50	7	9	50	50	13	8	50
	NOT REMARKABLE:	49	7	7	49	47	11	8	49
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	1	0	2	2	0	0
--AMYLOIDOSIS		0	0	*	0	0	0	0	1
--HYPERPLASIA, LYMPHOID		0	0	0	0	1	0	0	0
--AUTOLYZED		0	0	0	1	0	0	0	0
--MISSING		1	0	0	0	0	0	0	0

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=ALL;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	50	50	50	50	50	50	50	50
LN, MANDIBULAR (MN)	NUMBER EXAMINED:	50	7	9	50	50	15	8	50
	NOT REMARKABLE:	40	4	6	43	40	9	7	43
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	1	1	0	5	5	1	1
--CONGESTION/HEMORRHAGE		0	0	0	1	0	0	0	0
--AUTOLYZED		0	0	0	1	0	0	0	0
--MISSING		8	2	2	5	5	1	0	6
EYE (EY)	NUMBER EXAMINED:	50	7	9	50	50	14	8	50
	NOT REMARKABLE:	47	7	7	40	46	9	6	39
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	1	0	1	0	0	0
--CATARACT		0	0	0	1	1	0	0	0
--PHTHISIS		0	0	0	0	1	0	0	0
--AUTOLYZED		3	0	1	9	2	5	2	11
HARDERIAN GLAND (HG)	NUMBER EXAMINED:	50	7	10	50	50	15	8	50
	NOT REMARKABLE:	46	6	7	47	44	11	8	50
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	1	0	0	0	0	0
--B-ADENOMA		4	1	1	1	6	2	0	0
--HYPERPLASIA, FOCAL		0	0	1	0	0	1	0	0
--INFLAMMATION, CHRONIC		0	0	0	0	0	1	0	0
--AUTOLYZED		0	0	0	1	0	0	0	0
--MISSING		0	0	0	1	0	0	0	0
THYMUS (TH)	NUMBER EXAMINED:	50	7	9	50	50	14	8	50
	NOT REMARKABLE:	34	5	5	25	41	5	4	29
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	0	4	0	3	6	1	0
--AUTOLYZED		0	0	0	0	1	0	0	0
--MISSING		14	2	0	25	5	4	3	21

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=ALL;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER OF ANIMALS AFFECTED ---							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	50	50	50	50	50	50	50	50
MUSCLE, SKELETAL (SM)	NUMBER EXAMINED:	50	7	9	50	50	13	8	50
	NOT REMARKABLE:	50	7	6	47	47	12	8	49
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	1	0	1	0	0	0
--ATROPHY		0	0	0	2	0	0	0	0
--DEGENERATION		0	0	2	1	2	0	0	1
--LYMPHOCYTIC INFILTRATE		0	0	0	0	0	1	0	0
NERVE, SCIATIC (SN)	NUMBER EXAMINED:	50	7	9	50	50	13	8	50
	NOT REMARKABLE:	19	4	3	29	9	6	4	28
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	1	0	0	0	0	0
--DEGENERATION		29	2	5	21	38	6	4	22
--MISSING		2	1	0	0	3	1	0	0
SKIN (SK)	NUMBER EXAMINED:	50	7	9	50	50	13	8	50
	NOT REMARKABLE:	50	6	8	40	49	12	7	41
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	1	0	1	0	0	0
--B-TRICHOEPITHELIOMA		0	0	0	0	0	0	1	0
--EDEMA		0	1	0	10	0	0	0	9
--AUTOLYZED		0	0	0	0	0	1	0	0
MAMMARY, FEMALE (MF)	NUMBER EXAMINED:	0	0	0	0	50	13	9	50
	NOT REMARKABLE:	0	0	0	0	37	9	7	37
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	1	1	0	0
--M-CARCINOMA		0	0	0	0	0	0	1	0
--DILATATION, DUCT(S)		0	0	0	0	1	2	0	0
--LACTATION		0	0	0	0	4	1	0	0
--HYPERPLASIA, LOBULAR		0	0	0	0	3	0	0	0
--MISSING		0	0	0	0	6	0	1	13

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=ALL;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER OF ANIMALS AFFECTED ---							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	50	50	50	50	50	50	50	50
MARROW, FEMUR (FM)	NUMBER EXAMINED:	50	7	9	50	50	13	8	50
	NOT REMARKABLE:	46	5	7	50	24	10	7	48
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	2	0	0	1	0	1
--HYPERPLASIA, GRANULOCYTIC		1	0	0	0	0	1	0	0
--FIBROOSSEOUS CHANGE		1	0	0	0	25	1	0	0
--AUTOLYZED		2	1	0	0	1	0	1	0
--MISSING		0	0	0	0	0	0	0	1
BONE, FEMUR (FE)	NUMBER EXAMINED:	50	7	9	50	50	13	8	50
	NOT REMARKABLE:	49	7	8	50	47	13	8	50
--FIBROUS OSTEODYSTROPHY		0	0	1	0	3	0	0	0
--MISSING		1	0	0	0	0	0	0	0
HEMATO NEOPLASIA (HN)	NUMBER EXAMINED:	50	50	50	50	50	50	50	50
	NOT REMARKABLE:	45	44	42	49	41	34	41	48
--M-MALIGNANT LYMPHOMA, MIXED		0	3	2	0	1	1	0	0
--M-MALIGNANT LYMPHOMA, LYMPHOCYTIC		1	2	2	0	5	4	2	1
--M-MALIGNANT LYMPHOMA, HISTIOCYTIC		2	1	1	1	0	7	5	1
--M-MALIGNANT LYMPHOMA, UNDIFFERENTIATED		1	0	3	0	2	2	2	0
--M-AUTOLYZED NEOPLASM		1	0	0	0	1	2	0	0
SKIN, OTHER (SS)	NUMBER EXAMINED:	13	11	14	11	14	15	16	4
	NOT REMARKABLE:	10	8	12	7	14	12	16	2
--B-SEBACEOUS ADENOMA		1	0	0	0	0	0	0	0
--EDEMA		0	1	0	3	0	0	0	2
--ATROPHY		0	0	0	2	0	0	0	1
--ACANTHOSIS, FOCAL		0	0	0	0	0	1	0	0
--INFLAMMATION, GRANULOMATOUS, TAIL		0	0	0	1	0	0	0	0

** CONTINUED ON NEXT PAGE **

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEAT=ALL;FIXD=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION	--- NUMBER-OF-ANIMALS-AFFECTED ---							
SEX:	-------MALE-------				------FEMALE------			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
NUMBER:	50	50	50	50	50	50	50	50
** FROM PREVIOUS PAGE **								
SKIN, OTHER (SS) ..... NUMBER EXAMINED:	13	11	14	11	14	15	16	4
--INFLAMMATION, SUBACUTE, FOOT	0	1	0	0	0	1	0	0
--INFLAMMATION, CHRONIC	1	1	0	0	0	0	0	0
--ULCER, TAIL	0	0	0	1	0	0	0	0
--ULCER, PREPUCE	1	0	0	0	0	0	0	0
--ULCER, SHOULDER	0	0	1	0	0	0	0	0
--ULCER, EAR	0	0	1	0	0	0	0	0
--ULCER, NECK	1	0	0	0	0	0	0	0
--ULCER FOOT	0	0	0	0	0	1	0	0
--ESCHAR, EAR	0	0	1	0	0	0	0	0
SUBCUTANEOUS TIS (SQ) ..... NUMBER EXAMINED:	1	0	2	1	1	1	2	0
NOT REMARKABLE:	0	0	0	0	0	0	0	0
--M-FIBROSARCOMA	0	0	1	1	1	0	2	0
--M-LEIOMYOSARCOMA	1	0	0	0	0	0	0	0
--M-HEMANGIOSARCOMA	0	0	1	0	0	0	1	0
--M-SARCOMA, UNDIFFERENTIATED	0	0	0	0	0	1	0	0
PREPUTIAL GLAND (PG) ..... NUMBER EXAMINED:	1	5	3	2	0	0	0	0
NOT REMARKABLE:	0	0	1	0	0	0	0	0
--CYSTIC DUCT(S)	1	1	2	2	0	0	0	0
--ABSCESS	0	4	0	0	0	0	0	0
NOT REMARKABLE:	10	8	12	7	14	12	16	2
LN, OTHER(S) (LN) ..... NUMBER EXAMINED:	3	1	1	0	0	9	3	0
NOT REMARKABLE:	0	0	0	0	0	1	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)	2	1	1	0	0	7	3	0
--HYPERPLASIA, LYMPHOID	1	0	0	0	0	1	0	0

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=ALL;FIND=ALL;SUBSET=ALL

--- NUMBER-OF-ANIMALS-AFFECTED ---

ORGAN AND FINDING DESCRIPTION	SEX:	MALE				FEMALE			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	50	50	50	50	50	50	50	50
CAVITY, ABDOM (PC)	NUMBER EXAMINED:	2	1	0	1	2	1	0	1
	NOT REMARKABLE:	1	1	0	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	1	0	0	0
--M-MYXOSARCOMA		0	0	0	0	0	1	0	0
--FAT NECROSIS		1	0	0	0	1	0	0	1
--HEMORRHAGE		0	0	0	1	0	0	0	0
PENIS (PE)	NUMBER EXAMINED:	0	2	1	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0
--INFLAMMATION, NECROTIZING/SUPPURATIVE, PREPUCE		0	1	0	0	0	0	0	0
--INFLAMMATION, NECROTIZING/SUPPURATIVE		0	1	0	0	0	0	0	0
--SEMINAL PLUG		0	1	0	0	0	0	0	0
--ULCER, PREPUCE		0	0	1	0	0	0	0	0
HEAD, CORDAL (HC)	NUMBER EXAMINED:	1	0	0	0	0	0	0	0
	NOT REMARKABLE:	1	0	0	0	0	0	0	0

** END OF LIST **